NEC 32.2 (Vogelbaum) Glioblastoma, Part I: Surgical Management and Adjuncts

Advancing *Imaging* to enhance Surgery: from *image* to *information* guidance

Marco Riva[1,2] M.D., **Egesta Lopci**[3] M.D., Ph.D., **Lorenzo G. Gay**[2,4], **Marco Conti Nibali**[2,4] MD., **Marco Rossi**[2,4] M.D., **Tommaso Sciortino**[2,4] M.D., **Antonella Castellano**[5] M.D. Ph.D AND **Lorenzo Bello**[2,4] M.D.

1. Department of Medical Biotechnology and Translational Medicine, Università degli Studi di Milano, Via Festa del Perdono 7, 20122, Milan, ITALY.

2. Unit of Neurosurgery, Fondazione IRCCS Ca' Grande Ospedale Maggiore Policlinico, Via Francesco Sforza, 35, 20122 Milan, ITALY.

3. Unit of Nuclear Medicine, Humanitas Clinical and Research Center - IRCCS, Via Manzoni 56, 20089, Rozzano (MI), ITALY.

4. Department of Oncology and Hemato-Oncology, Via Festa del Perdono 7, 20122, Milan, ITALY.

5. Neuroradiology Unit and CERMAC, Vita-Salute San Raffaele University, IRCCS San Raffaele Scientific Institute, Via Olgettina 60, 20123, Milan, ITALY

List of the Authors' emails (and Twitter Accounts)

marco.riva@unimi.it (@mriva_eu); egesta.lopci@cancercenter.humanitas.it (@LopciEgesta); lorenzoggay@gmail.com; marco.continibali@gmail.com (@dr_mcn); rossi.marco@gmail.com; tsciortino11@gmail.com; castellano.antonella@hsr.it (@antocastella); lorenzo.bello@unimi.it

Corresponding Author
Marco Riva, M.D.

Disclosure Statement

The MRI protocol reported in Figure 1-2 has been performed in the context of the EDEN2020 (Enhanced Delivery Ecosystem for Neurosurgery in 2020) project, that received funding from the European Union's EU Research and Innovation programme Horizon 2020 under Grant Agreement no. 688279.

Synopsis [92 words]

Conventional MR imaging (cMRI) has an established role as a crucial disease parameter in the multidisciplinary management of Glioblastoma *guiding* diagnosis, treatment planning, assessment, and follow-up. Yet, cMRI cannot provide adequate *information* regarding tissue heterogeneity and the infiltrative extent beyond the contrast-enhancement.

Advanced MR and PET imaging and newer analytical methods are transforming *images* into data (*radiomics*) and providing non-invasive biomarkers of molecular features (*radiogenomics*), conveying to surgery an enhanced *information* for improving decision-making.

This review analyzes the shift from *image* to *information*-guidance that is relevant for the surgical treatment of glioblastoma.

Key Words

[Glioblastoma], [Surgery], [Magnetic Resonance Imaging (MRI)], [Positron Emission Tomography (PET)], [Presurgical Planning], [Image-guidance], [radiomics]

Key Points

- Glioblastomas have tissue heterogeneity and an infiltrative nature beyond the contrast-enhanced region that cannot be fully resolved with conventional imaging.
- Radiomics and radiogenomics are transforming images into mineable data, contributing in identifying biomarkers of molecular features with clinical relevance and leading a paradigm shift from *image*- to *information-guidance*.
- Advanced imaging can optimize the diagnostic workflow and the therapeutic strategies.

Abbreviations

AA: amino acid

ASL: arterial spin labelling

CET: contrast-enhancing tumor

DCE: dynamic contrast-enhanced

DSC: dynamic susceptibility contrast

DWI: diffusion-weighted imaging

EOR: extent of resection

FET: fluoroethyl-L-tyrosine

IDH: Isocitrate de-hydrogenase

GBM: glioblastoma multiforme

GTR: gross-total resection

METH: methionine

MGMT: O(6)-Methylguanine-DNA methyltransferase

MRI: Magnetic Resonance Imaging

MRS: Magnetic Resonance Spectroscopy

nCET: non contrast-enhancing tumor

PET: Positron Emission Tomography

PWI: perfusion-weighted imaging

RANO: response assessment in neuro-oncology

SNR: signal-to-noise ratio

WHO: World Health Organization

Introduction

Background

The continuous advancements of scanning procedures and processes for the extraction of quantitative features have revolutionized the traditional view of medical images as pictures intended solely for visual interpretation. These on-going improvements are toggling images into mineable data that can be analyzed to support clinical decisions; this practice has been termed *radiomics*[1].

The improved understanding of the genomic signatures underlying gliomas[2–4] led to the new Brain Tumor Classification[5]. Intense efforts have been undertaken to make imaging capable of depicting distinct phenotypes, of identifying biomarkers of molecular features, and of providing a quantitative report of the findings. This effort has been referred to as *radio-genomics*[6,7] .

Imaging is essential in the management of gliomas, providing morphological, functional and metabolic data that support the diagnosis, the treatment planning, the follow-up of the patient, and the response to therapies.

A paradigm shift: from image- to information-guidance in brain surgery

Image-guidance is a term to identify the use of imaging in brain surgery. The power of scanning and analytical methods have been rendering images an invaluable source of data, leading to a paradigm shift[8,9]: from *image-* to *information*-guided surgery.

The brain surgeon can employ refined imaging to guide the management of gliomas within an integrated analysis of various data regarding anatomical, functional, and histopathological characteristics. In the pursuit of precision medicine[10], validated biomarkers are essential to enable a tailored care.

It is also currently acknowledged that most solid tumors, including Glioblastomas (GBMs), have both spatial and temporal heterogeneity[11–15]. This heterogeneity cannot be fully resolved accurately, timely, and non-invasively. Such a lack of information can hamper the choice of the right type of treatment, including surgery and, especially, the targeted therapies available and under clinical development and validation[16].

This review analyzes the shift from *image* to *information*-guidance and the limitations that are still to challenge, with a distinct emphasis on the role and benefits for brain surgery of GBMs.

Current Evidence

Conventional MRI (cMRI)

Conventional Magnetic Resonance Imaging (cMRI) is the elective neuroradiological technique for the study of GBMs[16]. The cMRI assesses the T2/fluid-attenuated inversion-recovery (FLAIR) abnormality and the enhancement on postcontrast T1-weighted images, due to the extravasation of contrast agents through the abnormal tumor blood-brain barrier. cMRI typically depicts an enhancing, necrotic-appearing mass surrounded by non-enhancing signal abnormalities. Hemorrhage, cystic changes, or multicentric enhancements are also frequently present[17,18].

cMRI is accurate in providing essential morphological details of the tumor and of its adjacent neural and vascular structures. cMRI also assesses the disease burden, i.e. whether the tumor changes are restricted to one anatomical site or appear at a macroscopic level[19] as a multicentric disease. Considering the rapid growth and expansion and the infiltrative behavior of GBMs[20,21], cMRI also depicts the displacement of brain structures resulting from the mass effect. These features confidentially lead to a radiological diagnosis of GBMs in the vast majority of cases. However, differential diagnosis should still be considered with other intra-axial (metastasis, lower-grade gliomas, lymphoma) and non-neoplastic lesions (abscess, demyelinating diseases), that can have overlapping imaging findings and may eventually require further diagnostic work-up.

The contribution of cMRI to brain surgery

The *information* that cMRI conveys is pivotal for the initial therapeutic management, to establish the indication and the type of surgery, the surgical planning of the resection, and the assessment of the potential risks of the procedure[22]. cMRI is also advised within 48 hours from surgery to assess the extent of resection (EOR)[23]. EOR is among the most relevant prognostic factors for GBMs, as the maximal resection of the contrast-enhancing tumor (CET) on T1-weighted MRI has been consistently associated with more prolonged survival in both newly-diagnosed[24–32] and recurrent[33–37] GBMs. This evidence argues for surgery to pursue the gross-total resection of the enhancing solid tumor mass in patients with GBMs whenever feasible and safe[16]. Preventing new neurological deficits is a crucial priority since post-operative complications are a negative prognostic factor[38,39]. In the post-operative cMRI, Diffusion-weighted imaging (DWI) is essential to detect possible cytotoxic edema, reflecting ischemic alterations, at the margins of the resection

that eventually enhances after 48 hours. If imaging is performed after 48 hours, contrast enhancement may be misinterpreted as a residual tumor, potentially impacting future evaluations. cMRI is essential for the accurate diagnosis. It contributes to guide therapeutic decisions and monitor the disease status[40,41]. As such, cMRI has been consistently advocated as a crucial disease parameter in both clinico-surgical practice and clinical trials[16]. In this context, efforts to develop a standardized imaging protocol has also been made to reduce variability and increase reliability[42].

Clinical Relevance

The progress in the treatment of GBMs has been slower than that observed in the majority of the extracranial malignancies. GBMs inexorably develop ultimate treatment resistance. Before new therapeutics options and delivery strategies become clinically available, it is therefore essential to optimize current therapies to improve overall and progression-free survival, to preserve the quality of life throughout the disease and, with longer survival, to eventually benefit the patients with new emerging therapeutic options[16,43].

cMRI, contrast enhancement and the extent of resection

The primary therapeutic management of GBMs consists of the surgical resection of the contrast-enhancing tumor (CET) followed by adjuvant therapies[16,44]. The gross-total resection (GTR) of the enhancing tumor is associated with longer survival in both adult and elderly subjects[32,45,46]. GTR can thus be regarded as the neurosurgical standard of care. Despite extensive efforts to reach a total resection of the CET components with several intraoperative technologies and adjuncts, the potential gains from improved resection of the CET seem currently plateauing.

Resection with clear margins is a common concept in surgical oncology. However, it is virtually unfeasible for GBMs because the neoplastic cells remain in the macroscopically normal-appearing brain tissue due to their highly infiltrative nature[19,47,48]. GBMs are highly infiltrative tumor, with neoplastic cells extending beyond the contrast-enhancing lesion. Retrospective case-series studies also reported an improved survival of patients who received resection of the not-CET (nCET) of GBMs as depicted by the T2/FLAIR sequence[49–52]. These studies reported an additional prognostic benefit of 5-13 months over patients who received resection merely of the CET. Although the quality of evidence is not yet robust due to the number of enrolled subjects and the retrospective mono-institutional study design, these initial results claims for reconsidering the definition of the

EOR. In particular, what can be considered a *total* resection? Has a so-called supratotal resection[53–55] to be pursued in patients with GBMs?

Collaterally, different studies employed slightly different thresholds for defining the resection; as a result, qualitative definitions of gross-, sub-, near-total are found, arbitrarily corresponding to 90, 95, 99% EOR. Therefore, caution must be used when comparing different studies using qualitative definitions. A precise quantitative measure for the EOR or alternative reporting methods, such as the residual tumor volume[30,56], are advocated to agree on the measure that most reliably describes the disease burden of pathobiological relevance. It is also essential to tailor the definition of *supratotal* when applied to GBMs to find a shared definition that can be employed for a multi-institutional confirmation of the initial clinical evidence. To precisely define the extent of disease beyond the pathological enhancement is also mandatory for avoiding unnecessary risks to the patients and for improving the prognostic impact of surgery.

As a result, it is thus a strong priority to enhance the radiological detection of residual tissue in post-operative cMRIs, to also discriminate vital tumor from post-surgical abnormalities[57]. It is further relevant to investigate the non-contrast enhancing tumor (nCET) components[58,59], to accurately depict and monitor them non-invasively with imaging. The nCET components have overlapping signal features with non-neoplastic abnormalities, such as edema, on T2/FLAIR sequences, hampering an accurate differential diagnosis. The nCET subregions of GBMs are not habitually resected, but they are often the primary site of recurrence or progression[60].

These arguments must also be framed within a clear understanding of the association of the maximal EOR with the molecular subgroups for survival, which is essential for counseling patients and clinical-surgical decision-making.

In this regard, a recent retrospective multi-institutional study reported a median survival of 37.3 months of subjects, younger than 65 years, receiving a complete CET resection with less than 5.4 ml residual nCET, as measured on post-operative T2/FLAIR cMRI, of pathologically proven GBMs. The younger patients with complete CET and near-total (median 90% resection) nCET resection and an IDH–wild-type tumor showed an overlapping survival with patients with IDH-mutant tumors within the first three years of treatments. These results were confirmed after adjusting for other clinical and molecular prognostic variables and with two validation sets from different institutes. This study thus represents a new robust source of evidence that the surgical resection of both CET and nCET on cMRI has a prognostic impact in the management of younger

(<65 years) patients with GBMs, independently from IDH and MGMT status. These results set the momentum for the proposal for an updated surgical strategy. This strategy keeps as a priority to maximize the EOR to the morpho-functional limits and to avoid post-operative morbidity, with the aid of advanced pre- and intra-operative imaging modalities and intraoperative stimulation mapping[61–65].

As for what imaging is concerned, given the survival benefit that is emerging from aggressive surgery, a better characterization of signal abnormalities additional to CE and accurate differential diagnosis of these from other pathological entities is thus of paramount relevance to optimize the available therapeutic strategies. cMRI is limited in resolution for such a characterization to guide a more aggressive resection. It is therefore needed to improve the delineation of nCET from edema and of tumor parts with an intact blood-brain barrier that therefore lacks enhancement[66,67]. A better characterization of eloquent subcortical structures can also be beneficial for the pre-operative risk assessment and to also contribute to safety. Advanced Imaging is advocated to overcome current limitations of cMRI in depicting the actual tumor extent, additional to the CET, and the eloquent white matter structures. It is essential to avoid both false-negative and false-positive radiological reports, which can be detrimental for safety (*not halting the resection before morpho-functional eloquent landmarks*) and for the EOR (*halting the resection before it can be considered complete*), respectively. To develop better methods to detect non-enhancing lesion burden would optimize surgical and radiation planning while minimizing risks to the truly healthy parenchyma.

Advanced *Imaging* for improving *information* guidance

Advanced imaging is asked to address distinct unmet challenges in neurosurgical oncology to increase the amount and quality of information that cMRI can convey to surgery for better guidance: **i)** to improve the spatial resolution of the lesion tissue heterogeneity and microstructural features (tumor core, infiltrative areas, micro-environment), including a thorough characterization of nCET; **ii)** to better describe eloquent white matter structures[68,69]; **iii)** to investigate and validate imaging surrogates of molecular features (radio-genomics); **iv)** to develop computational analytical methods (radiomics), testing sensitivity, specificity and accuracy in detecting signal abnormalities that are not discernible to the human eye; **v)** to research acquisition and evaluation methods to identify and quantify the tumor changes in response to the different types of therapies (i.e., surgery, radiation therapy, chemotherapy, immunotherapy, and targeted therapies). It will

also be beneficial to match eventual findings of advanced features with cMRI for the clinical practice and to develop standardized protocols. These efforts could ease widespread use across centers and multi-institutional studies, individualize the acquisition to the specific needs and clinical queries about the patient at a given time and optimize examination time to be clinically feasible, with a reduction in patient discomfort for repeated scans over time.

The available imaging armamentarium and expected developing pipelines are **i)** the application of quantitative imaging approaches, such as the analysis of texture features (i.e., a pattern of local variations in image intensity) on cMRI images[70]; **ii)** advanced MRI techniques; **iii)** different imaging modalities, such as Positron-Emission Tomography (PET).

Advanced MR imaging

Advanced MRI techniques such as diffusion MRI (dMRI), perfusion-weighted imaging (PWI) and MR spectroscopy (^{1}H-MRS) can provide a visual depiction and quantitative measurement of the pathophysiological characteristics of the tumor.

Diffusion MRI (dMRI)

The dMRI-derived mean diffusivity (MD), or apparent diffusion coefficient (ADC), is considered a measure of tumor cellularity, as the diffusion of extracellular water is abnormally restricted when tumor cells proliferate and disrupt the normal tissue architecture[71]. Quantitative ADC measurements in GBMs have been reported to predict the methylation status of the MGMT promoter and patients' survival[72–74]. Other metrics derived from diffusion tensor imaging (DTI) may help characterizing the extent of tumor infiltration beyond the apparent margins on cMRI, thus reflecting glioma cells' invasion[75] according to the GBM molecular phenotype[76].

Functional magnetic resonance imaging (fMRI) and diffusion MRI tractography

Functional MRI (fMRI) and diffusion MRI tractography have become an integral part of the preoperative assessment and intraoperative guidance for brain gliomas. These techniques provide information on the anatomical-functional organization of eloquent cortical areas and subcortical connections near or within a tumor to aid the maximal safe resection. 'Classical' DTI tractography approaches were proven to be a valid and highly sensitive tool for localizing eloquent subcortical areas in glioma patients[68]. Newer diffusion models and tractography techniques, based on high

angular resolution diffusion-weighted imaging (HARDI), have been developed to enhance the accuracy of MR tractography for glioma surgery[68] [**Figure 1**].

Perfusion-weighted imaging (PWI)

PWI allows to measure changes associated with neoangiogenesis in GBMs both at first diagnosis [**Figure 1-2**] and after treatment[77–80]. The dynamic susceptibility contrast (DSC)-derived rCBV is the most validated parameter[81] with a reliable correlation with microvascular changes induced by neoangiogenesis, such as the increase of microvessel density[82,83]. Dynamic contrast-enhanced (DCE) is a further PWI technique that reflects a combination of tissue intra-vascular compartment volume (fractional volume of the intravascular compartment, v_p), microvessel permeability (volume transfer constant, K^{trans}), and extravascular-extracellular space (v_e)[78,84,85]. DCE allows a multiparametric quantification of tumor microvascular features. Notably, PWI-derived metrics have been shown to predict key molecular signatures such as EGFRvIII status in EGFR-amplified GBMs with high accuracy, both alone or in combination with other conventional and advanced MRI features [cMRI, DWI, DSC and SWI[86,87]; PWI[88–91]. Finally, in the setting of GBMs follow-up, PWI-derived quantitative parameters separating viable tumor from treatment changes demonstrate relatively good accuracy in individual studies, with pooled sensitivities and specificities of 90% and 88% for DSC and 89% and 85% for DCE[92].

MR spectroscopy (MRS)

^{1}H-MRS provides metabolic biomarkers that complement MRI anatomical and physiological information in gliomas[93]. ^{1}H-MRS has been used to detect in vivo the intratumoral accumulation of 2-hydroxyglutarate (2HG), a metabolite that is present at high levels in IDH-mut GBMs[94–97]. Although still technically challenging, 2HG-MRS has demonstrated excellent diagnostic performance in the prediction of IDH mutant glioma, with pooled sensitivity and specificity of 95% and 91%, respectively[98]. These findings open a new scenario for the non-invasive monitoring of the biological effects of new targeted therapies such as mutant-IDH1 inhibitors in glioma patients[99].

Specific studies are available that thoroughly reviewed each step leading to the generation of quantitative radiomics output from conventional and advanced MRI data (i.e., image acquisition,

processing, segmentation of tumor regions of interest, features extraction, data analyses and validation[1,70,100,101].

Advanced MRI and tumor microenvironment (TME): spatial habitat imaging

Applying advanced mathematical modeling, it is also possible to segment tumors into subregions containing clusters of voxels with similar quantitative radiomics features, that represent and quantify tumor microenvironment heterogeneity[102]. Imaging of the tumor microenvironment (TME), or spatial habitat imaging, has been applied mainly on cMRI images. Nevertheless, it can be virtually extended to any imaging modality, including PWI and dMRI, to scrutinize specific features to infer tumor behavior from imaging characteristics. Intratumoral heterogeneity of oxygen metabolism combined with variable patterns of neovascularization, as depicted by advanced MRI, has been shown to affect the landscape of TMEs in GBM and correlate with prognosis[103,104].

Molecular Imaging with Amino Acid PET (AA-PET)

Molecular imaging based on nuclear medicine compounds retains three amino acid tracers as principal representatives for glioma assessment[105,106]: [11C-methyl]-methionine (11C-METH), O-(2-[18F]fluoroethyl)-L-tyrosine (18F-FET) and 3,4-dihydroxy-6-[18F]fluoro-L-phenylalanine (18F-FDOPA). Their mechanism of uptake is related to the L amino acid transport system and their application in brain tumor imaging relies on the acknowledged enhancement of amino acid transport and protein synthesis in cancer cells, which are crucial for cell proliferation and growth, as well as extracellular matrix production in gliomas[107–109].

Evidence-based recommendations on the use of amino acid tracers in glioma imaging with PET[105] and practice guidelines about the procedure standards[106] have been recently released. In principal, amino acid PET (AA-PET) is utilized at primary glioma diagnosis, allowing tumor differentiation, glioma grading and prognostication, as well as definition of tumor delineation [**Figure 3**] and can guide targeting optimal biopsy sites [**Figure 4**] thanks to the definition of "hot spots" or areas with maximum tracer uptake[110–116].

The role of AA-PET has been maintained also in the light of the new WHO classification 2016 for brain tumors[117], thanks to the significant differences observed in imaging variables obtained from 11C-METH PET and 18F-FET PET in gliomas with different mutational status or molecular characteristics[113,114,118,119]. Conversely, more contradictory results have been reported for 18F-

FDOPA PET[120,121], which might present with paradoxically increased uptake in IDH1 positive diffuse gliomas.

The use of imaging parameters to detect intrinsic glioma characteristics non-invasively has largely involved PET radiomics and more recently it has implicated artificial intelligence[122,123]. Although investigated at a lower extent compared to corresponding MRI radiomics, encouraging results on AA-PET suggest an accuracy of 93% in predicting grade-based texture features in GBM[124], and an accuracy of 90.66% in predicting glioma overall survival[125].

Overall 90% of primary brain tumors are detectable by AA-PET as hypermetabolic lesions, with a small proportion of cases resulting iso- or even hypometabolic compared to normal brain uptake[126,127]. Regardless of morphological characteristics, the information provided by PET proves still valuable and clear photopenic (i.e. hypometabolic) areas defined in negative 18F-FET PET scans correspond to different prognostic outcomes in grade III and IV gliomas[127].

In comparison to conventional and advanced MRI, AA-PET retains a complementary role and allows a more precise distinction of gliomas due to the improved specificity and metabolic characterization[116,128], even in case of recurrence or when assessing the response from pseudoprogression or other treatment-related changes. For presumed recurrent glioma, the modality performs with a high sensitivity (range 96–100%), and diagnostic accuracy (range 82–94%)[126,129]. Applying hybrid 11C-METH PET/MRI, AA-PET outperformed MRI and differentiated progression versus pseudoprogression with a 97.1% sensitivity and 93.3% specificity compared to 86.1% sensitivity and 71.4% specificity for MRI[128,129].

Discussion

The information yield of advance imaging to brain surgery

Neurosurgery can take the momentum of advanced imaging to improve surgical practice and match the oncological needs of the patient in a multidisciplinary context. Neurosurgery can also represent an essential validation ground of these techniques, linking non-invasive biomarkers to histo-molecular data from targeted tissue samples.

An accurate and precise integrated histo-molecular diagnosis at a given time is mandatory for treatment decisions and prognosis, especially in a time claiming for precision medicine[130,131], since therapeutic options become increasingly depending on molecular features for both clinical and experimental management[132,133].

The molecular features currently relevant (i.e., IDH 1-2, MGMT methylation) for the integrated diagnosis are generally homogeneously represented throughout the tumor tissue[115,134,135]. Therefore, a sampling error resulting in misclassification of acknowledged tumor molecular features that have current therapeutic and prognostic relevance[5], is unlikely both during open surgery and bioptic procedures if adequately performed. cMRI guides the appropriate site for sampling, targeting areas of enhancement likely containing viable tumor cells, preferably avoiding necrotic areas or adjacent nonneoplastic brain. Metabolic PET imaging can also support the targeting, increasing the diagnostic yield of stereotactic biopsies[110,115,134].

However, spatial and temporal heterogeneity of GBMs is increasingly characterized and considered from the genomic to the phenotypic level[13,15,48,132,136,137]. The potential translation of these discoveries into improved patients' outcomes is yet to come. Validated and reproducible methods are thus needed to resolve both intralesional (spatial) and longitudinal (temporal) heterogeneity of these tumors, that is both related to tumor natural history and the treatment-related effects. In particular, advanced imaging methods can contribute effectively to target sampling to areas with biological relevance for an impactful clinical strategy[138].

In fact, by clinical convention, current sampling is still guided by the enhancement of cMRI. This policy assumes a homogeneous representation that summarizes the tumor as a whole with a single representative profile and imaging signature of the instead heterogeneous features of the tumor[139,140]. This surgical strategy lacks specific information to distinguish many of the genetically distinct tumor populations that can reside within a single tumor[141].

Favoring the CET, the surgical targeting neglects the clonal populations and the heterogeneity of nCET areas[141]. Both cMRI and surgical targeting currently underdiagnosed these areas, despite they represent the primary targets of adjuvant therapies, the main site of recurrence[60] and they likely harbor therapeutic targets remaining elusive after resection or biopsy of the CET[67,139]. Since both tumor and non-tumoral pathophysiological changes coexist within the nCET area, caution must still be taken to claim surgical targeting of both normal-appearing (on cMRI) or non-tumoral white matter.

The lack of discriminative power of cMRI is particularly evident when a differential diagnosis between recurrence and treatment-induced changes mimicking progression is requested. Such signal abnormalities (i.e., pseudoprogression and radiation-induced necrosis[142]) can occur in up to 36% of patients with high-grade gliomas [143,144]. In this circumstance, the agreement among

pathologists for diagnosing a recurrent disease is far from being optimal, with a reported agreement rate of 36-68%[145,146]. This reported rate is partially due to tissue heterogeneity and a mixture of viable tumor cells and treatment-related changes that cMRI cannot correctly discriminate. This lack of information leaves surgery a target with a likely low-confidence of being representative of the driving tumor populations, which, however, share identical conventional radiological phenotypes with non-tumor changes[147]. Increasing the quality and quantity of non-invasive presurgical data can influence the decision-making with enhanced information and, eventually, lead to a better outcome.

Brain surgery must and can take advantage of advanced imaging to tailor the surgical targeting of representative tumor areas that are biologically and clinically relevant. Instead of a cloud targeting of abnormal areas of cMRI, an *information-guided* surgical strategy avoids both unneeded risk exposure and a low diagnostic yield. It also supports treatment decisions at a given time throughout the disease course more robustly. The multidisciplinary management of these subjects must also be agreed on consistent radiological protocols, comprehensive of cMRI and selected advanced MR sequences. Such standardized adaptive protocols should match the oncological need at a given time point and, at the same time, constrain scanning and analytical times. Standardization will also be essential to increase study comparisons and reproducibility and, also, to pursue and validate cut-off values of quantitative measures.

Final Remarks

A subject with GBM undergoes serial MR scans, from clinical presentation, through the peri-operative time, to the adjuvant therapeutic stage. Histomolecular characterization of the tumor is essential for effective and timely decision-making. Current limitations exist in resolving the intra-tumoral spatial heterogeneity and the longitudinal evolving mutational landscape over time, as it depends on the analysis of invasive tissue sampling through surgery. Such invasive sampling results limited to the time and site when and where, respectively, the tissue is collected from a highly heterogeneous tumor.

Acknowledging the role of cMRI as established, advanced imaging is building a consistent momentum for non-invasive profiling of tissue composition in addition to known pathological landmarks. Brain surgery can thus benefit from enhanced information to tailor surgical indication and to guide sampling, within multidisciplinary management. Targeting the tumor areas with the more relevant biological features and, thus, with a likely more meaningful clinical impact, will be essential to address oncological needs more adequately. A better informed surgical strategy is expected to lower sampling errors further and to represent the validation benchmark of radiogenomic findings, while keeping the patient's safety as a critical priority. Leaving the role of liquid biopsy of the central nervous system's tumors apart[148], advanced imaging can be regarded as a watchful non-invasive sentinel aiding the clinical surveillance in patrolling the disease status and providing the clinician with the enhanced information needed for an improved individualized care.

Clinics Care Points

- MR Imaging is essential in the management of gliomas, supporting diagnosis, surgical planning, treatment assessment and follow-up.
- The current neurosurgical standard of care of Glioblastomas (GBMs) aims at the total resection of the contrast-enhancing lesion, as depicted by conventional MRI.
- Conventional MR imaging cannot fully resolved the spatial and temporal heterogeneity, and the highly infiltrative nature beyond the contrast-enhanced region of GBMs.
- Advance MR and PET Imaging contributes to improving the understanding, the characterization and the differential diagnosis of distinct tumor habitats and the non-contrast-enhanced regions.
- Neurosurgery can benefit from enhanced *information* from imaging to target the tumor areas with the most relevant biological features.
- Advanced imaging can support the multi-disciplinary decision-making to precisely address oncologic needs with an individualized approach, pursuing a meaningful clinical impact.

References

1. Gillies R.J., Kinahan P.E., Hricak H. Radiomics: Images Are More than Pictures, They Are Data. Radiology 2016;278(2):563–77.
2. Cancer Genome Atlas Research Network., Brat D.J., Verhaak R.G.W., et al. Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. N Engl J Med 2015;372(26):2481–98.
3. Yan H., Parsons D. W., Jin G., et al. IDH1 and IDH2 Mutations in Gliomas. N Engl J Med 2009;360(8):765–73.
4. Hegi M.E., Diserens A.C., Gorlia T., et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. N Engl J Med 2005;352(10):997–1003.
5. Louis D.N., Perry A., Reifenberger G., et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016;131(6):803–20.
6. Castellano A., Falini A. Progress in neuro-imaging of brain tumors. Curr Opin Oncol 2016;28(6):484–93.
7. Pope W.B. Genomics of Brain Tumor Imaging. Neuroimaging Clin N Am 2015;25(1):105–19.
8. Muragaki Y., Iseki H., Maruyama T., et al. Information-guided surgical management of gliomas using low-field-strength intraoperative MRI. Acta Neurochir Suppl 2011;109:67–72.
9. Fukuya Y., Ikuta S., Maruyama T., et al. Tumor recurrence patterns after surgical resection of intracranial low-grade gliomas. J Neurooncol 2019;144(3):519–28.
10. Collins F.S., Varmus H. A new initiative on precision medicine. N Engl J Med 2015;372(9):793–5.
11. Patel A.P., Tirosh I., Trombetta J.J., et al. Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. Science 2014;344(6190):1396–401.
12. Neftel C., Laffy J., Filbin M.G., et al. An Integrative Model of Cellular States, Plasticity, and Genetics for Glioblastoma. Cell 2019;178(4):835-849.e21.
13. Sottoriva A., Spiteri I., Piccirillo S.G.M., et al. Intratumor heterogeneity in human glioblastoma reflects cancer evolutionary dynamics. Proc Natl Acad Sci U S A 2013;110(10):4009–14.

14. Johnson Brett E., Mazor T., Hong C., et al. Mutational analysis reveals the origin and therapy-driven evolution of recurrent glioma. Science 2014;343(6167):189–93.
15. Barthel F.P., Johnson K.C., Varn F.S., et al. Longitudinal molecular trajectories of diffuse glioma in adults. Nature 2019;576(7785):112–20.
16. Wen P.Y., Weller M., Lee E.Q., et al. Glioblastoma in Adults: A Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) Consensus Review on Current Management and Future Directions. Neuro Oncol 2020. *In press*.
17. Henson J.W., Gaviani P., Gonzalez R.G.. MRI in treatment of adult gliomas. Lancet Oncol 2005:167–75.
18. Ly K. I., Wen P.Y., Huang R.Y. Imaging of Central Nervous System Tumors Based on the 2016 World Health Organization Classification. Neurol Clin 2020:95–113.
19. Sahm F., Capper D., Jeibmann A., et al. Addressing diffuse glioma as a systemic brain disease with single-cell analysis. Arch Neurol 2012;69(4):523–6.
20. Giese A., Westphal M. Glioma invasion in the central nervous system. Neurosurgery 1996:235–52.
21. Cuddapah V.A.., Robel S., Watkins S., et al. A neurocentric perspective on glioma invasion. Nat Rev Neurosci 2014:455–65.
22. Riva M., Bello L. Low-grade glioma management: A contemporary surgical approach. Curr Opin Oncol 2014;26(6).
23. Vogelbaum M.A., Jost S., Aghi M.K., et al. Application of novel response/progression measures for surgically delivered therapies for gliomas: Response Assessment in Neuro-Oncology (RANO) working group. Neurosurgery 2012;70(1):234–43.
24. Chaichana K.L., Jusue-Torres I., Navarro-Ramirez R.., et al. Establishing percent resection and residual volume thresholds affecting survival and recurrence for patients with newly diagnosed intracranial glioblastoma. Neuro Oncol 2013;16(1):113–22.
25. Sanai N., Polley M.Y., McDermott M.W., et al. An extent of resection threshold for newly diagnosed glioblastomas: Clinical article. J Neurosurg 2011;115(1):3–8.
26. Stummer W., Reulen H.J., Meinel T., et al. Extent of resection and survival in glioblastoma multiforme: Identification of and adjustment for bias. Neurosurgery 2008;62(3):564–74.

27. Stummer W., Pichlmeier U., Meinel T., et al. Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: a randomised controlled multicentre phase III trial. Lancet Oncol 2006;7(5):392–401.
28. Marko N.F., Weil R.J., Schroeder J.L., et al. Extent of Resection of Glioblastoma Revisited: Personalized Survival Modeling Facilitates More Accurate Survival Prediction and Supports a Maximum-Safe-Resection Approach to Surgery. J Clin Oncol 2014;32(8):774–82.
29. Lacroix M., Abi-Said D., Fourney D. R., et al. A multivariate analysis of 416 patients with glioblastoma multiforme: Prognosis, extent of resection, and survival. J Neurosurg 2001;95(2):190–8.
30. Grabowski M.M., Recinos P.F., Nowacki A.S., et al. Residual tumor volume versus extent of resection: Predictors of survival after surgery for glioblastoma. J Neurosurg 2014;121(5):1115–23.
31. W Kreth F., Thon N., Simon M., et al. Gross total but not incomplete resection of glioblastoma prolongs survival in the era of radiochemotherapy. Ann Oncol 2013;24:3117–23.
32. Brown T.J., Brennan M.C., Li M., et al. Association of the extent of resection with survival in glioblastoma a systematic review and meta-Analysis. JAMA Oncol 2016;2(11):1460–9.
33. Oppenlander M.E., Wolf A.B., Snyder L.A., et al. An extent of resection threshold for recurrent glioblastoma and its risk for neurological morbidity: Clinical article. J Neurosurg 2014;120(4):846–53.
34. Ringel F., Pape H., Sabel M., et al. Clinical benefit from resection of recurrent glioblastomas: results of a multicenter study including 503 patients with recurrent glioblastomas undergoing surgical resection. Neuro Oncol 2015;18(1):96–104.
35. Bloch O., Han S.J., Cha S., et al. Impact of extent of resection for recurrent glioblastoma on overall survival: Clinical article. J Neurosurg 2012;117(6):1032–8.
36. Suchorska B., Weller M., Tabatabai G., et al. Complete resection of contrast-enhancing tumor volume is associated with improved survival in recurrent glioblastoma—results from the DIRECTOR trial. Neuro Oncol 2016;18(4):549–56.

37. Pessina F., Navarria P., Cozzi L., et al. Role of surgical resection in recurrent glioblastoma: prognostic factors and outcome evaluation in an observational study. J Neurooncol 2017;131(2):377–84.
38. Stummer W., Tonn J.C.., Mehdorn H.M., et al. Counterbalancing risks and gains from extended resections in malignant glioma surgery: a supplemental analysis from the randomized 5-aminolevulinic acid glioma resection study. Clinical article. J Neurosurg 2011;114(3):613–23.
39. Gulati S., Jakola A.S., Nerland U.S., et al. The risk of getting worse: Surgically acquired deficits, perioperative complications, and functional outcomes after primary resection of glioblastoma. World Neurosurg 2011:572–9.
40. Wen P.Y., Macdonald D.R., Reardon D.A., et al. Updated response assessment criteria for high-grade gliomas: Response assessment in neuro-oncology working group. J Clin Oncol 2010:1963–72.
41. Okada H., Weller M., Huang R., et al. Immunotherapy response assessment in neuro-oncology: A report of the RANO working group. Lancet Oncol 2015:e534–42.
42. Ellingson B.M., Bendszus M.., B. Jerrold., et al. Consensus recommendations for a standardized Brain Tumor Imaging Protocol in clinical trials. Neuro Oncol 2015;17(9):1188–98.
43. Lim M., Xia Y., Bettegowda C., et al. Current state of immunotherapy for glioblastoma. Nat Rev Clin Oncol 2018:422–42.
44. Stupp R., Mason W.P., Van Den Bent M.J., et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352(10):987–96.
45. Molinaro A.M., Hervey-Jumper S., Morshed R.A., et al. Association of Maximal Extent of Resection of Contrast-Enhanced and Non-Contrast-Enhanced Tumor with Survival within Molecular Subgroups of Patients with Newly Diagnosed Glioblastoma. JAMA Oncol 2020;6(4).
46. Conti Nibali M., Gay L.G., Sciortino T.., et al. Surgery For Glioblastoma in Elderly Patients. Neurosurg Clin N Am 2020. *In press*.
47. Daubon T., Léon C.., Clarke K.., et al. Deciphering the complex role of thrombospondin-1 in glioblastoma development. Nat Commun 2019;10(1).

48. Boyé K., Pujol N., Alves D. Isabel., et al. The role of CXCR3/LRP1 cross-talk in the invasion of primary brain tumors. Nat Commun 2017;8(1).
49. Li Yan M., Suki D., Hess K., et al. The influence of maximum safe resection of glioblastoma on survival in 1229 patients: Can we do better than gross-total resection? J Neurosurg 2016;124(4):977–88.
50. Pessina F., Navarria P., Cozzi L.., et al. Maximize surgical resection beyond contrast-enhancing boundaries in newly diagnosed glioblastoma multiforme: is it useful and safe? A single institution retrospective experience. J Neurooncol 2017;135(1):129–39.
51. Beiko J., Suki D.., Hess K.R., et al. IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection. Neuro Oncol 2013;16(1):81–91.
52. Jain R., Poisson L.M., Gutman D., et al. Outcome prediction in patients with glioblastoma by using imaging, clinical, and genomic biomarkers: Focus on the nonenhancing component of the tumor. Radiology 2014;272(2):484–93.
53. Yordanova Y.N., Moritz-Gasser S., Duffau H. Awake surgery for WHO grade II gliomas within “noneloquent” areas in the left dominant hemisphere: Toward a “supratotal” resection - Clinical article. J Neurosurg 2011;115(2):232–9.
54. de Leeuw Charles N., Vogelbaum M.A. Supratotal resection in glioma: a systematic review. Neuro Oncol 2019;21(2):179–88.
55. Rossi M., Ambrogi F., Gay L.G., et al. Is supratotal resection achievable in low-grade gliomas? Feasibility, putative factors, safety, and functional outcome. J Neurosurg 2019:1–14.
56. Kotrotsou A., Elakkad A., Sun J., et al. Multi-center study finds postoperative residual non-enhancing component of glioblastoma as a new determinant of patient outcome. J Neurooncol 2018;139(1):125–33.
57. Ellingson B.M., Abrey L.E., Nelson S.J., et al. Validation of postoperative residual contrast-enhancing tumor volume as an independent prognostic factor for overall survival in newly diagnosed glioblastoma. Neuro Oncol 2018;20(9):1240–50.
58. Navarria P., Reggiori G., Pessina F., et al. Investigation on the role of integrated PET/MRI for target volume definition and radiotherapy planning in patients with high grade glioma. Radiother Oncol 2014;112(3):425–9.

59. Lasocki X A., Gaillard X F. Non-Contrast-Enhancing Tumor: A New Frontier in Glioblastoma Research. AJNR Am J Neuroradiol 2019 ;40(5):758-765.
60. John F., Bosnyák E., Robinette N.L., et al. Multimodal imaging-defined subregions in newly diagnosed glioblastoma: impact on overall survival. Neuro Oncol 2018;21(2):264–73.
61. De Witt Hamer P.C., Robles Santiago G., Zwinderman A.H., et al. Impact of intraoperative stimulation brain mapping on glioma surgery outcome: A meta-analysis. J Clin Oncol 2012:2559–65.
62. Bello L., Riva M., Fava E., et al. Tailoring neurophysiological strategies with clinical context enhances resection and safety and expands indications in gliomas involving motor pathways. Neuro Oncol 2014;16(8).
63. Riva M., Fava E., Gallucci M., et al. Monopolar high-frequency language mapping: Can it help in the surgical management of gliomas? A comparative clinical study. J Neurosurg 2016;124(5).
64. Bello L., Rossi M., Conti Nibali M., et al. Neurophysiology of language and cognitive mapping. Neurophysiology in Neurosurgery. Elsevier; 2020. p. 101–12.
65. Bello L., Rossi M., Conti Nibali M., et al. Functional approach to brain tumor surgery: awake setting. Neurophysiology in Neurosurgery. Elsevier; 2020. p. 257–69.
66. Sarkaria J.N., Hu L.S., Parney I.F., et al. Is the blood–brain barrier really disrupted in all glioblastomas? A critical assessment of existing clinical data. Neuro Oncol 2017;20(2):184–91.
67. Price S J., Jena R., Burnet N G., et al. Improved Delineation of Glioma Margins and Regions of Infiltration with the Use of Diffusion Tensor Imaging: An Image-Guided Biopsy Study. AJNR Am J Neuroradiol 2006;27(9):1969-74.
68. Castellano A., Cirillo S., Bello L., et al. Functional MRI for Surgery of Gliomas. Curr Treat Options Neurol 2017;19(10).
69. Sanvito F., Caverzasi E., Riva M., et al. fMRI-Targeted High-Angular Resolution Diffusion MR Tractography to Identify Functional Language Tracts in Healthy Controls and Glioma Patients. Front Neurosci 2020;14.
70. Fathi Kazerooni A., Bakas S., Saligheh R.H., et al. Imaging signatures of glioblastoma molecular characteristics: A radiogenomics review. J Magn Reson Imaging 2019.

71. Hygino da Cruz L. C., Vieira I.G., Domingues R.C. Diffusion MR Imaging: An Important Tool in the Assessment of Brain Tumors. Neuroimaging Clin N Am 2011:27–49.
72. Romano A., Calabria L. F., Tavanti F., et al. Apparent diffusion coefficient obtained by magnetic resonance imaging as a prognostic marker in glioblastomas: Correlation with MGMT promoter methylation status. Eur Radiol 2013;23(2):513–20.
73. Sunwoo L., Choi Seung H., Park Chul K.., et al. Correlation of apparent diffusion coefficient values measured by diffusion MRI and MGMT promoter methylation semiquantitatively analyzed with MS-MLPA in patients with glioblastoma multiforme. J Magn Reson Imaging 2013;37(2):351–8.
74. Moon W.J., Choi J.W., Roh H.G., et al. Imaging parameters of high grade gliomas in relation to the MGMT promoter methylation status: The CT, diffusion tensor imaging, and perfusion MR imaging. Neuroradiology 2012;54(6):555–63.
75. Sternberg E. J., Lipton M. L., Burns J. Utility of diffusion tensor imaging in evaluation of the peritumoral region in patients with primary and metastatic brain tumors. Am J Neuroradiol 2014:439–44.
76. Price S.J., Allinson K., Liu H., et al. Less invasive phenotype found in isocitrate dehydrogenase-mutated glioblastomas than in isocitrate dehydrogenase wild-type glioblastomas: A diffusion-tensor imaging study. Radiology 2017;283(1):215–21..
77. Shiroishi M.S., Boxerman J.L., Pope W.B. Physiologic MRI for assessment of response to therapy and prognosis in glioblastoma. Neuro Oncol 2015;18(4):467–78.
78. Anzalone N., Castellano A., Cadioli M., et al. Brain Gliomas: Multicenter Standardized Assessment of Dynamic Contrast-enhanced and Dynamic Susceptibility Contrast MR Images. Radiology 2018;287(3):933–43.
79. Álvarez-Torres M., Juan-Albarracín J., Fuster-Garcia E., et al. Robust association between vascular habitats and patient prognosis in glioblastoma: An international multicenter study. J Magn Reson Imaging 2020;51(5):1478–86.
80. Patel P., Baradaran H., Delgado D., et al. MR perfusion-weighted imaging in the evaluation of high-grade gliomas after treatment: a systematic review and meta-analysis. Neuro Oncol 2017;19(1):118–27.

81. Shiroishi M.S., Castellazzi G., Boxerman J.L., et al. Principles of T2∗-weighted dynamic susceptibility contrast MRI technique in brain tumor imaging. J Magn Reson Imaging 2015:296–313.
82. Barajas Jr R.F., Phillips J.J., Parvataneni R., et al. Regional variation in histopathologic features of tumor specimens from treatment-naive glioblastoma correlates with anatomic and physiologic MR Imaging. Neuro Oncol 2012;14(7):942–54.
83. Sadeghi N., D'Haene N., Decaestecker C., et al. Apparent diffusion coefficient and cerebral blood volume in brain gliomas: Relation to tumor cell density and tumor microvessel density based on stereotactic biopsies. Am J Neuroradiol 2008;29(3):476–82.
84. Essig M., Nguyen T.B., Shiroishi M.S., et al. Perfusion MRI: The five most frequently asked clinical questions. Am J Roentgenol 2013.
85. Heye A.K., Culling R.D., Valdés Hernández Maria Del C., et al. Assessment of blood-brain barrier disruption using dynamic contrast-enhanced MRI. A systematic review. NeuroImage Clin 2014:262–74.
86. Kickingereder P., Radbruch A., Burth S., et al. MR Perfusion-derived hemodynamic Parametric response Mapping of Bevacizumab efficacy in recurrent glioblastoma. Radiology 2016;279(2):542–52.
87. Ellingson B.M., Gerstner E.R., Smits M., et al. Diffusion MRI phenotypes predict overall survival benefit from Anti-VEGF monotherapy in recurrent glioblastoma: Converging evidence from phase II trials. Clin Cancer Res 2017;23(19):5745–56.
88. Arevalo-Perez J., Thomas A. A., Kaley T., et al. T1-weighted dynamic contrast-enhanced MRI as a noninvasive biomarker of epidermal growth factor receptor VIII status. Am J Neuroradiol 2015;36(12):2256–61.
89. Politi L. S., Brugnara G., Castellano A., et al. T1-weighted dynamic contrast-enhanced MRI is a noninvasive marker of epidermal growth factor receptor VIII status in cancer stem cell-derived experimental glioblastomas. Am J Neuroradiol 2016:E49–51.
90. Akbari H., Bakas S., Pisapia J.M., et al. In vivo evaluation of EGFRvIII mutation in primary glioblastoma patients via complex multiparametric MRI signature. Neuro Oncol 2018;20(8):1068–79.

91. Tykocinski E.S., Grant R.A., Kapoor G.S., et al. Use of magnetic perfusion-weighted imaging to determine epidermal growth factor receptor variant III expression in glioblastoma. Neuro Oncol 2012;14(5):613–23.
92. Patel P., Baradaran H., Delgado D., et al. MR perfusion-weighted imaging in the evaluation of high-grade gliomas after treatment: a systematic review and meta-analysis. Neuro Oncol 2017;19(1):118–27.
93. Chaumeil M.M., Lupo J.M., Ronen S.M. Magnetic Resonance (MR) Metabolic Imaging in Glioma. Brain Pathol 2015;25(6):769–80.
94. Andronesi O.C., Kim G.S., Gerstner E., et al. Detection of 2-hydroxyglutarate in IDH-mutated glioma patients by in vivo spectral-editing and 2D correlation magnetic resonance spectroscopy. Sci Transl Med 2012;4(116).
95. Choi C., Ganji S.K., DeBerardinis R.J., et al. 2-Hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. Nat Med 2012;18(4):624–9.
96. Choi C., Raisanen J.M., Ganji S.K., et al. Prospective longitudinal analysis of 2-hydroxyglutarate magnetic resonance spectroscopy identifies broad clinical utility for the management of patients with IDH-mutant glioma. J Clin Oncol 2016;34(33):4030–9.
97. Branzoli F., Di Stefano A.L., Capelle L., et al. Highly specific determination of IDH status using edited in vivo magnetic resonance spectroscopy. Neuro Oncol 2017;20(7):907–16.
98. Suh C.H., Kim H.S., Jung S.C., et al. 2-Hydroxyglutarate MR spectroscopy for prediction of isocitrate dehydrogenase mutant glioma: a systemic review and meta-analysis using individual patient data. Neuro Oncol 2018;20(12):1573–83.
99. Andronesi O.C., Arrillaga-Romany I.C., Ly K.I., et al. Pharmacodynamics of mutant-IDH1 inhibitors in glioma patients probed by in vivo 3D MRS imaging of 2-hydroxyglutarate. Nat Commun 2018;9(1).
100. Castellano A., Falini A. Progress in neuro-imaging of brain tumors. Curr Opin Oncol 2016:484–93.
101. Smits M., Van Den Bent M.J. Imaging correlates of adult glioma genotypes. Radiology 2017:316–31.
102. Gatenby R.A., Grove O., Gillies R.J. Quantitative imaging in cancer evolution and ecology. Radiology 2013:8–15.

103. Stadlbauer A., Zimmermann M., Doerfler A., et al. Intratumoral heterogeneity of oxygen metabolism and neovascularization uncovers 2 survival-relevant subgroups of IDH1 wild-type glioblastoma. Neuro Oncol 2018;20(11):1536–46.
104. Stadlbauer A., Oberndorfer S., Zimmermann M., et al. Physiologic MR imaging of the tumor microenvironment revealed switching of metabolic phenotype upon recurrence of glioblastoma in humans. J Cereb Blood Flow Metab 2020;40(3):528–38.
105. Albert N.L., Weller M., Suchorska B., et al. Response Assessment in Neuro-Oncology working group and European Association for Neuro-Oncology recommendations for the clinical use of PET imaging in gliomas. Neuro Oncol 2016;18(9):1199–208.
106. Law I., Albert N.L., Arbizu J., et al. Joint EANM/EANO/RANO practice guidelines/SNMMI procedure standards for imaging of gliomas using PET with radiolabelled amino acids and [18 F]FDG: version 1.0. Eur J Nucl Med Mol Imaging 2019;46(3):540–57.
107. Deykin D., Balko C., Isselbacher K.J. Sugar and Amino Acid Transport by Cells in Culture — Differences between Normal and Malignant Cells. N Engl J Med 1972:929–33.
108. Ishiwata K., Kubota K., Murakami M., et al. Re-evaluation of Amino Acid PET Studies: Can the Protein Synthesis Rates in Brain and Tumor Tissues Be Measured In Vivo? J Nucl Med 1993;34(11):1936–43.
109. la Fougère C., Suchorska B., Bartenstein P., et al. Molecular imaging of gliomas with PET: Opportunities and limitations. Neuro Oncol 2011;13(8):806–19.
110. Pirotte B., Goldman S., Massager N., et al. Combined use of 18F-fluorodeoxyglucose and 11C-methionine in 45 positron emission tomography-guided stereotactic brain biopsies. J Neurosurg 2004;101(3):476–83.
111. Torii K., Tsuyuguchi N., Kawabe J., et al. Correlation of amino-acid uptake using methionine PET and histological classifications in various gliomas. Ann Nucl Med 2005;19(8):677–83.
112. Pöpperl G., Kreth F.W., Mehrkens J.H., et al. FET PET for the evaluation of untreated gliomas: Correlation of FET uptake and uptake kinetics with tumour grading. Eur J Nucl Med Mol Imaging 2007;34(12):1933–42.
113. Lopci E., Riva M., Olivari L., et al. Prognostic value of molecular and imaging biomarkers in patients with supratentorial glioma. Eur J Nucl Med Mol Imaging 2017;44(7):1155–64.

114. Riva M., Lopci E., Castellano A., et al. Lower Grade Gliomas: Relationships Between Metabolic and Structural Imaging with Grading and Molecular Factors. World Neurosurg 2019;126:e270–80.
115. Sciortino T., Fernandes B., Conti Nibali M., et al. Frameless stereotactic biopsy for precision neurosurgery: diagnostic value, safety, and accuracy. Acta Neurochir (Wien) 2019.
116. Castello A., Riva M., Fernandes B., et al. The role of 11C-methionine PET in patients with negative diffusion-weighted magnetic resonance imaging. Nucl Med Commun 2020:1. Doi: 10.1097/MNM.0000000000001202.
117. Suchorska B., Giese A., Biczok A., et al. Identification of time-to-peak on dynamic 18F-FET-PET as a prognostic marker specifically in IDH1/2 mutant diffuse astrocytoma. Neuro Oncol 2018;20(2):279–88.
118. Verger A., Stoffels G., Bauer E.K., et al. Static and dynamic 18F–FET PET for the characterization of gliomas defined by IDH and 1p/19q status. Eur J Nucl Med Mol Imaging 2018;45(3):443–51.
119. Bauer E.K., Stoffels G., Blau T., et al. Prediction of survival in patients with IDH-wildtype astrocytic gliomas using dynamic O-(2-[18F]-fluoroethyl)-l-tyrosine PET. Eur J Nucl Med Mol Imaging 2020;47(6).
120. Verger A., Metellus Ph., Sala Q., et al. IDH mutation is paradoxically associated with higher 18F-FDOPA PET uptake in diffuse grade II and grade III gliomas. Eur J Nucl Med Mol Imaging 2017;44(8):1306–11.
121. Cicone F., Carideo L., Scaringi C., et al. 18 F-DOPA uptake does not correlate with IDH mutation status and 1p/19q co-deletion in glioma. Ann Nucl Med 2019;33(4):295–302.
122. Lohmann P., Kocher M., Steger J., et al. Radiomics derived from amino-acid PET and conventional MRI in patients with high-grade gliomas. Q J Nucl Med Mol Imaging 2018:272–80.
123. Sotoudeh H., Shafaat O., Bernstock J.D., et al. Artificial intelligence in the management of glioma: Era of personalized medicine. Front Oncol 2019. Doi: 10.3389/fonc.2019.00768.
124. Li-Chun H.K., Chen C.Y., Lo Chung M. Quantitative glioma grading using transformed gray-scale invariant textures of MRI. Comput Biol Med 2017;83:102–8.

125. Nie D., Lu J., Zhang H., et al. Multi-Channel 3D Deep Feature Learning for Survival Time Prediction of Brain Tumor Patients Using Multi-Modal Neuroimages. Sci Rep 2019;9(1).
126. Glaudemans A.W.J.M., Enting R.H., Heesters M.A.A.M., et al. Value of 11C-methionine PET in imaging brain tumours and metastases. Eur J Nucl Med Mol Imaging 2013:615–35. Doi:
127. Galldiks N., Unterrainer M., Judov N., et al. Photopenic defects on O-(2-[18F]-fluoroethyl)-L-tyrosine PET: clinical relevance in glioma patients. Neuro Oncol 2019;21(10):1331–8.
128. Bonm A.V., Ritterbusch R., Throckmorton P., et al. Clinical Imaging for Diagnostic Challenges in the Management of Gliomas: A Review. J Neuroimaging 2020:139–45.
129. Deuschl C., Kirchner J., Poeppel T.D., et al. 11C–MET PET/MRI for detection of recurrent glioma. Eur J Nucl Med Mol Imaging 2018;45(4):593–601.
130. Weller M., Stupp R., Hegi M.E., et al. Personalized care in neuro-oncology coming of age: Why we need MGMT and 1p/19q testing for malignant glioma patients in clinical practice. Neuro Oncol 2012;14(SUPPL.4). Doi: 10.1093/neuonc/nos206.
131. Prados M.D., Byron S.A., Tran N.L., et al. Toward precision medicine in glioblastoma: the promise and the challenges. Neuro Oncol 2015;17(8):1051–63.
132. Ene Chibawanye I., Fine Howard A. Many Tumors in one: A daunting therapeutic prospect. Cancer Cell 2011:695–7.
133. Snuderl M., Fazlollahi L., Le Long P., et al. Mosaic amplification of multiple receptor tyrosine kinase genes in glioblastoma. Cancer Cell 2011;20(6):810–7.
134. Eigenbrod S., Trabold R., Brucker D., et al. Molecular stereotactic biopsy technique improves diagnostic accuracy and enables personalized treatment strategies in glioma patients. Acta Neurochir (Wien) 2014;156(8):1427–40.
135. Mader M.M., Rotermund R., Martens T., et al. The role of frameless stereotactic biopsy in contemporary neuro-oncology: molecular specifications and diagnostic yield in biopsied glioma patients. J Neurooncol 2019;141(1):183–94.
136. Brennan C.W., Verhaak R.G.W., McKenna A., et al. The somatic genomic landscape of glioblastoma. Cell 2013;155(2):462.

137. Klughammer J., Kiesel B., Roetzer T., et al. The DNA methylation landscape of glioblastoma disease progression shows extensive heterogeneity in time and space. Nat Med 2018;24(10):1611–24.
138. Rathore S., Akbari H., Rozycki M., et al. Radiomic MRI signature reveals three distinct subtypes of glioblastoma with different clinical and molecular characteristics, offering prognostic value beyond IDH1. Sci Rep 2018;8(1).
139. Barajas R.F., Hodgson J. G., Chang J.S., et al. Glioblastoma multiforme regional genetic and cellular expression patterns: Influence on anatomic and physiologic MR imaging. Radiology 2010;254(2):564–76. Doi: 10.1148/radiol.09090663.
140. Itakura H., Achrol A.S., Mitchell L.A., et al. Magnetic resonance image features identify glioblastoma phenotypic subtypes with distinct molecular pathway activities. Sci Transl Med 2015;7(303).
141. Hu L.S., Ning S., Eschbacher J.M., et al. Radiogenomics to characterize regional genetic heterogeneity in glioblastoma. Neuro Oncol 2016;19(1):128–37.
142. Leao D. J., Craig P. G., Godoy L. F., et al. Response assessment in neuro-oncology criteria for gliomas: Practical approach using conventional and advanced techniques. Am J Neuroradiol 2020:10–20.
143. Abbasi A.W., Westerlaan H.E., Holtman G.A., et al. Incidence of Tumour Progression and Pseudoprogression in High-Grade Gliomas: a Systematic Review and Meta-Analysis. Clin Neuroradiol 2018;28(3):401–11.
144. Brandes A.A., Franceschi E., Tosoni A., et al. MGMT promoter methylation status can predict the incidence and outcome of pseudoprogression after concomitant radiochemotherapy in newly diagnosed glioblastoma patients. J Clin Oncol 2008;26(13):2192–7.
145. Holdhoff M., Ye X., Piotrowski A.F., et al. The consistency of neuropathological diagnoses in patients undergoing surgery for suspected recurrence of glioblastoma. J Neurooncol 2019;141(2):347–54.
146. Kim J.HE., Bae J.Y.., Han J.H., et al. Pathologic diagnosis of recurrent glioblastoma: Morphologic, immunohistochemical, and molecular analysis of 20 paired cases. Am J Surg Pathol 2012;36(4):620–8.

147. Prah M.A., Al-Gizawiy M.M., Mueller W.M., et al. Spatial discrimination of glioblastoma and treatment effect with histologically-validated perfusion and diffusion magnetic resonance imaging metrics. J Neurooncol 2018;136(1):13–21.
148. Seoane J., De Mattos-Arruda L., Le Rhun E., et al. Cerebrospinal fluid cell-free tumour DNA as a liquid biopsy for primary brain tumours and central nervous system metastases. Ann Oncol 2019;30(2):211–8.

Figure Legends

Figure 1

Advanced MRI of a 64 year-old male with GBM (grade IV), IDH1 wild-type, and MGMT promoter methylation. Axial *FLAIR* (**A)** and *T1-w* post-gadolinium (**B)** images demonstrate an inhomogeneous lesion in the left occipital lobe with strong but irregular ring enhancement surrounding a central nonenhancing necrotic core. A satellite, small enhancing nodule is also evident (open arrows). (**C**) *Dynamic Susceptibility Contrast PWI* relative cerebral blood volume (rCBV) and (**D**) *Dynamic-Contrast Enhanced PWI* volume transfer constant (K^{trans}) maps demonstrate significantly increased perfusion and leakiness along the enhancing margins of the lesion. (**E**) Pre-operative, three-dimensional HARDI Q-ball tractography reconstructions superimposed on post-gadolinium *T1-w* images demonstrate with high resolution the entire course of the optic pathways (orange) and their relationships with the tumor tissue: the left optic radiation runs very closely to the lateral margin of the lesion and of the satellite nodule. Surgery was performed with intraoperative Visual Evoked Potentials and tractography reconstructions available on the neuronavigation platform. (**F**) Post-operative contrast-enhanced *T1-w* images with superimposed preoperative tractography show a complete resection of both the lesions, with the left optic radiation aligned to the functional limits of resection along the border of the surgical cavity.

Figure 2

Advanced MRI of a 42 year-old female with GBM (grade IV), IDH2 mutated *without* MGMT promoter methylation. Axial *FLAIR* (**A)** and *T1-w* post-gadolinium (**B)** images demonstrate an inhomogeneous lesion in the left parietal lobe with intense, irregular enhancement with a peripheral rim surrounding a central nonenhancing necrotic core. (**C**) *Dynamic Susceptibility Contrast PWI* relative cerebral blood volume (rCBV) and (**D**) *Dynamic-Contrast Enhanced PWI* volume transfer constant (K^{trans}) maps demonstrate a moderate increase of perfusion and permeability along the enhancing margins of the lesion. (**E**) Three-dimensional rendering of preoperative HARDI Q-ball tractography reconstruction of the arcuate fascicle (red) superimposed on post-gadolinium *T1-w* images show the relationship of this tract with the lesion: the deep portion of the tract runs in close contiguity to the deep margin of the lesion. Surgery was performed

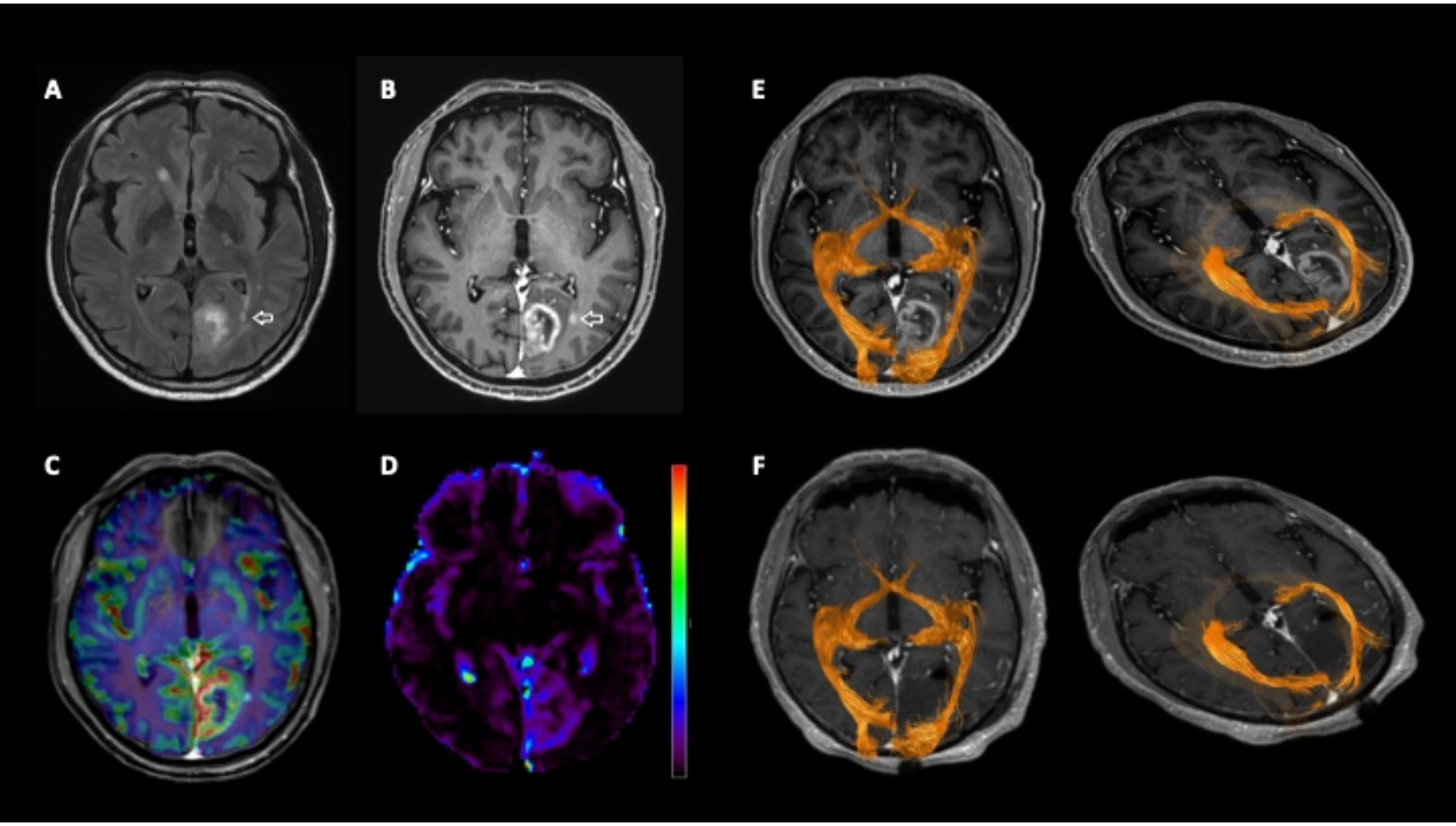
with intra-operative neurophysiological and neuropsychological monitoring and mapping techniques under the asleep-awake-asleep anesthesia regimen[64]. (**F**) Post-operative contrast-enhanced *T1-w* images with superimposed preoperative tractography show a complete resection of the lesion, with the left arcuate fascicle lining the border of the surgical cavity, thus aligned to the functional limits of resection.

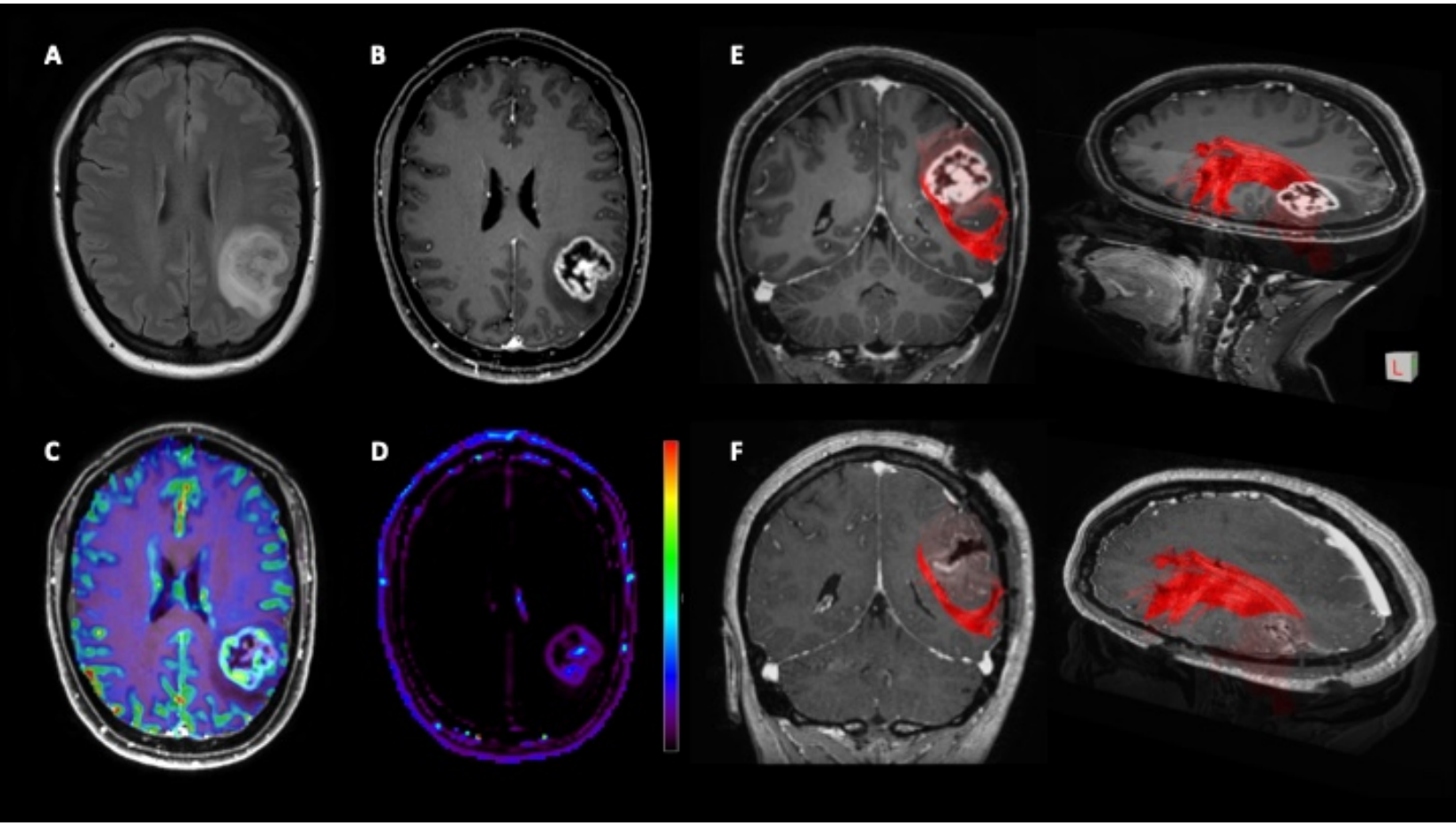
Figure 3

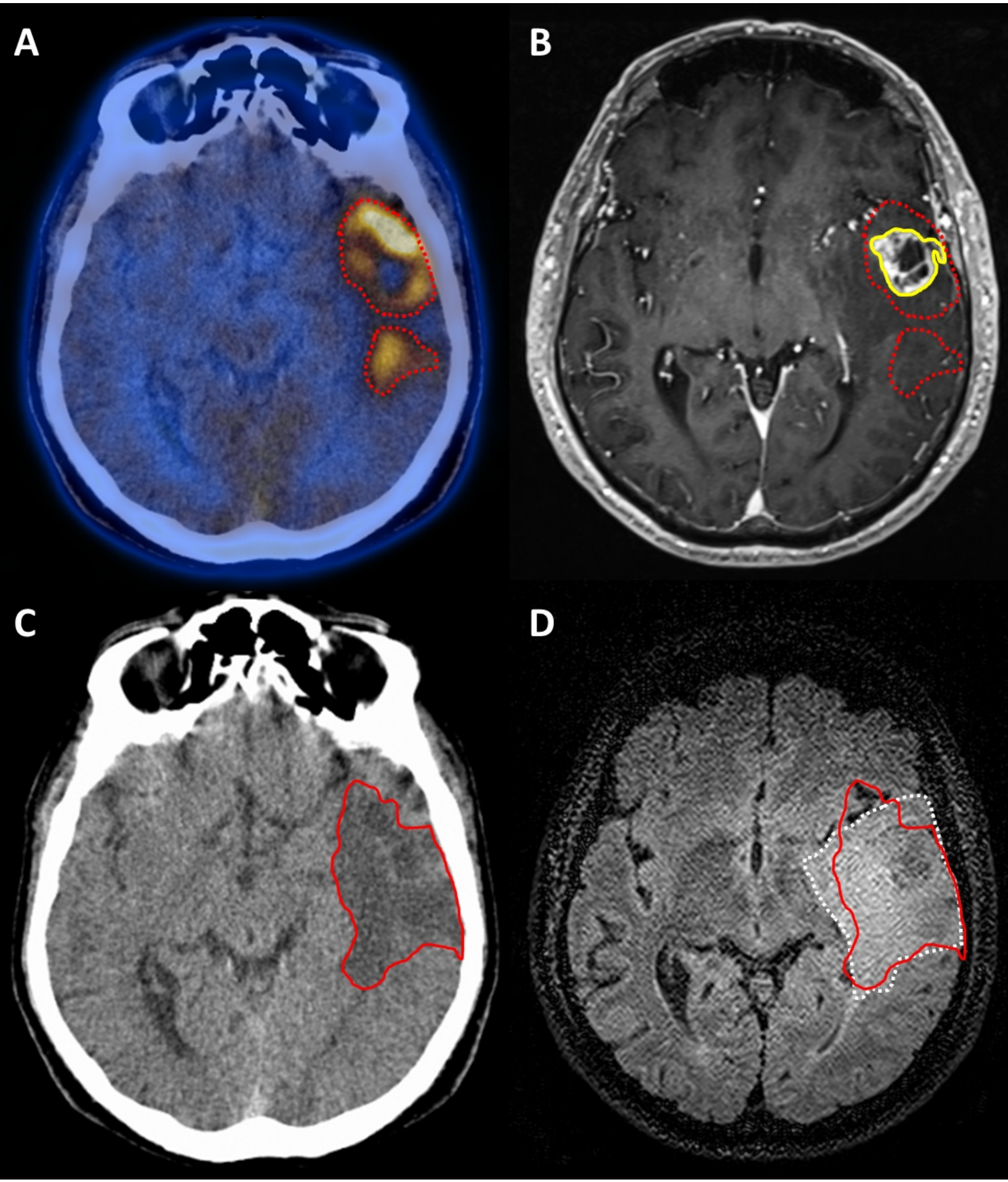
Imaging findings of a 75 year-old male with GBM (grade IV), IDH1 wild-type, MGMT promoter methylation and 11p/19q co-deletion. The co-registered 11C-METH PET/CT (**A**), gadolinium-enhanced MRI (**B**), axial low-dose CT (**C**) and FLAIR (**D**) are shown. The areas with intense PET tracer accumulation (SUVmax 4.9; SUVratio 3.5) are defined with red dotted lines (**A,B**) and superimposed on the corresponding region on MRI (**B**), in comparison to the extent of the enhanced area (*yellow line*; **B**). Similarly, the hypodense/edematous area on localization CT (*red line*; **C**) is placed in comparison to the altered FLAIR signal (*white dotted line*; **D**).

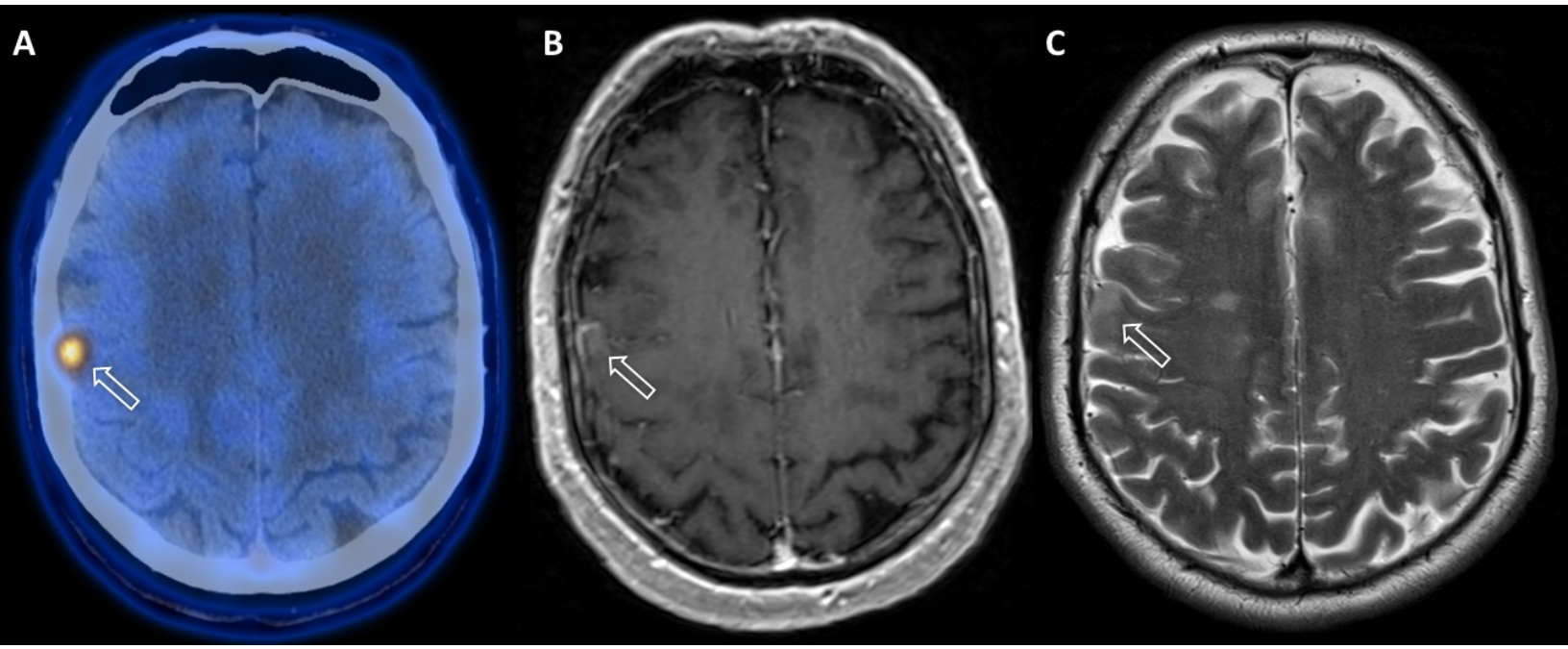
Figure 4

Illustration of a "hot-spot" on 11C-METH PET/CT (**A**), in comparison with the corresponding gadolinium-enhanced MRI (**B**) and T2-weighted views (**C**). The lesion indicated with the white hollowed arrows corresponds to an Anaplastic Astrocytoma (grade III), IDH1 wild-type, not methylated and not co-deleted. The focal uptake on PET (SUVmax 5.5; SUVratio 5) is clearly visible, while a faint signal is seen on gadolinium enhanced (**B**) or T2-weighted MRI (**C**).


A
B
E
C
D
F


A
B
E
C
D
F
L


A
B
C
D


A
B
C