Advanced MR Image Biomarkers and Updated Genomic Biomarkers for Brain Gliomas: Technical Point and Clinical Application

Kyung Mi Lee[1], Eui Jong Kim[2], Ji Hye Jang[2], and Woo Suk Choi[2]
[1]*Kyung Hee University Hospital, Seoul, Seoul, Korea,* [2]*Kyung Hee University Hospital, Seoul, Korea*

Purpose

The DWI, DSC, DCE of brain tumors are now widely used in the diagnosis and post-treatment evaluation of brain tumors. In the clinical setting, functional, quantitative and qualitative approaches with genomic biomarkers are being applied in practice, but there are several pitfalls with all of these approaches. Understanding and applying the different imaging techniques and genomic biomarkers in a multi-parametric algorithmic fashion in the clinical and research settings can be shown to increase diagnostic specificity and confidence.

Outline of content

1.Introduction

- WHO classification of glioma: astrocytoma, oligodendroglioma, mixed oligoastrocytoma, ependymoma
- grading of brain gliomas: correlate with the therapeutic plan, prognosis and treatment response
- pathologic criteria for high grade glioma : mitosis, nuclear atypia, necrosis (based on conventional MRI), cellularity (on DWI, ADC), angiogenesis (on PWI)

2. **MR imaging biomarkers** [1]

1) Diffusion weighted imaging (DWI) and Apparent diffusion coefficient (ADC)

: reduction in extracellular space and the high nuclear to cytoplasmic ratios of tumor→ free water molecules' diffusivity is restricted → lower ADC values suggesting high-grade lesions

: biologic property – diffusivity of water

: pathophysiologic correlates – tissue architecture (cell density, extracellular space tortuosity, gland formation, cell membrane integrity, necrosis)

2) Dynamic contrast-enhanced (DCE) perfusion MR

: DCE techniques are the most commonly applied imaging techniques for the characterization of microvascular structure and function.

: rapid, serial images are acquired during the administration of an intravenous contrast agent

: biologic property – contrast medium uptake rate in tissues which is influenced by plasma volume fraction perfusion and transfer rates extracellular volume

: pathophysiologic correlates – vessel permeability, vessel density, perfusion, tissue cell fraction, plasma volume

: IAUC, Ktrans, Kep, Ve, Vp

3) Dynamic susceptibility contrast (DSC) perfusion MR

: in tumors, neoangiogenesis → distorted vascular beds → excessive proportion of blood vessels → abnormal morphology and flow characteristics

: on DSC-MRI, CBF (cerebral blood flow) can be performed by comparison of the contrast concentration changes in a feeding artery with the changes in tissue voxels → CBV (cerebral blood volume), CBF, MTT (mean transit times), vessel size index

: biologic property – blood volume and blood flow

: pathophysiologic correlates –blood flow, tumor grade, vessel density, vessel diameter

: clinical application - high-grade vs. low-grade glioma, high-grade glioma vs. metastasis vs. lymphoma, abscess vs. hemangioblastoma vs. metastasis, radiation necrosis vs. tumor recurrence, tumor-progression vs treatment related change vs. infarction (cytotoxic edema)

4) 2 hydroxyglutarate(HG) MR spectroscopic imaging : detection of IDH-mutated gliomas [2]

3. **Genomic biomarkers**

: Glial progenitor cells ----EGFR amplification(~35%), TP53 mutation(~30%), PTEN mutation(~25%), NF1 alteration(~20%), LOH 10p(~70%), 10q(~70%) ----------→ Primary glioblastoma(GBM)

: Glial progenitor cells ----IHD1 mutation(>85%) → common precursor cells → 1) if TP 53 mutation(>65%) → diffuse astrocytoma → LOH 10q (>60%)→ secondary glioblastoma

: Glial progenitor cells ----IHD1 mutation(>85%) → common precursor cells → 2) if loss 1p/19q(>75%) → oligodendroglioma → anaplastic oligodenroglioma

1) IDH (isocitrate dehydrogenase) mutation

: major and independent prognostic factor, associated secondary GBM [3], detect by using 2HG MR spectroscopy [2]

2) MGMT (O^6-methylguanine-DNA methyltransferase) promotor methylation

: lack of MGMT in the cell → subsequent to incorrect pairing → DNA damage signaling → cell death

: resistance to alkylating agent (temozolomide) cancer therapy → predictive for response to temozolomide in GBM [4]

3) EGFR (epidermal growth factor receptor) mutation

: primary contributor genome to tumor initiation and progression in GBM

4) PTEN (phosphatase and tensin homologue) mutation

: blocking the downstream pathways of EGFR mediated cellular proliferation

: GFR expression combined with PTEN gene loss → promotes increased angiogenesis and increased tumor perfusion → poor prognosis, also influence responses to EGFR-targeted therapy

5) 1p/19q co-deletion

: tightly linked to the oligodendroglial lineage, associated with better prognosis

Summary

Quantitative genomic biomarkers with advanced MR image biomarkers are essential in diagnosing of brain tumors, monitoring treatment response and differentiation of radiation necrosis and tumor recurrence.

Ref) 1. Anwar R.P. et al. Multiparametric imaging of tumor response to therapy. Radiology 2010;256(2):348-364 2. Changho Choi et al. 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. Nature Medicine 2012;18:624-629 3. Yan H. et al. IDH1 and IDH2 mutations in gliomas. N Engl J Med 2009;360:765-773 4. Alba 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 Oncology 2008;26(13)