Brain Tumors: Radiologic Perspective

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The job of the neuroradiologist in the work-up of brain tumors has quite changed in the last two decades. It is no longer limited to evaluating structural abnormality and to describe location and morphological features such as calcification, cyst formation, hemorrhage, vascularization, contrast enhancement, perilesional vasogenic edema and mass effect. Development of advanced MR methods has changed imaging in neuro-oncology from the purely anatomy-based discipline of the early 90s to one that must evaluate metabolic, hemodynamic, microscopic and functional properties(1).

The modern neuroradiologist plays a pivotal role in the management of brain tumors from early *in vivo* presurgical diagnosis to treatment planning and after-treatment surveillance. It would be impossible to treat neuro-oncology patients without taking advantage of multiparametric MR methods all together. Integration of anatomic MR imaging with MR perfusion, diffusion, spectroscopy and functional imaging is providing more accurate tissutal and metabolic characterization of brain masses that has become indispensable especially in evaluating response to therapy.

Cerebral metastases represent about 50% of brain tumors. Gliomas represent 40% of primary cerebral neoplasms and they are the most intriguing group of brain cancer. It is important to considerate infiltrating WHO-II and WHO-III gliomas separately from invasive WHO-IV glioblastomas (GBM), because management is very different.

Infiltrating WHO-II gliomas are slowly and constantly growing neoplasms that occur in relatively young adult patients living a regular life. Low grade gliomas (LGG) are associated with minimal or no neurological deficits for several years. LGG are infiltrative masses that do not compress the adjacent functional brain tissue. They do not interrupt or dislocate white matter fascicules. However, they are not stable (benign) tumors. The classical radiological criteria proposed by the RANO group are not appropriate to monitor diffuse LGG growth(2). An objective and accurate 3D volumetric

measurement on T2-FLAIR with computation of an individual growth rate before and after each management step should be performed(3). Multiparametric MR parameters (measured with MR perfusion, diffusion and spectroscopy) may increase the sensitivity of detecting tumor transformation. Eventually LGG will transform in secondary GBM; demise usually occurs in less than 10 years(4).

The WHO classification does not recognize that many infiltrating gliomas have an "intermediate" behavior nor that there is a continuum between WHO-II and WHO-III gliomas. Advanced MR methods are good to illustrate the heterogeneous biological nature of infiltrating gliomas within each subtype (astrocytoma, oligoastrocytoma, mixed glioma). Cerebral blood volume (rCBV) and permeability measured with MR perfusion are indices of tumor angiogenesis. In infiltrating gliomas rCBV has been inversely correlated with overall patient survival(5). Choline signals measured with Proton MR spectroscopic imaging correlate with cell density, while NAA signal loss is an index of tumor infiltration.

Neurosurgeons and neuroncologists are aware of the importance of including imaging data for the evaluation of disease status and are demanding comprehensive assessment of glioma biology. Recent advancement in molecular biology have shown that time is ready to move forward toward a revisited multimodal classification that will be more appropriate for clinical practice(6). Analysis of molecular data supports a system that reclassifies WHO II and III infiltrating gliomas by combining histologic and molecular data. **Codeletion of chromosome 1p and 19q** replaces the distinction in cytological type (i.e. astrocytoma, oligodendroglioma and mixed glioma) as the primary class discriminator within WHO II and III grades. This results in a four class model that is biologically-accurate and clinically relevant. Patients with chromosome 19p/19q codeletion have a longer overall survival (87 and 76.6 months for WHO-II and III respectively) than those who are chromosomally-intact (58.1 and 31.3 months), regardless of the grade(6).

Other molecular factors such as isocitrate dehydrogenase (IDH) and methylation of the promoter for O6-methylguanine-DNA methyltransferase (*MGMT*) have been demonstrated to correlate with survival, but their use in stratification of patients is more limited than 19p/19q codeletion. Mutations

in the active site of IDH were found in a large percentage of young patients with WHO-II and WHO-III gliomas and in most secondary GBM. Patients with IDH mutations have a significantly improved prognosis with a median overall survival of 3.8 years as compared to 1.1 years for patients with wild-type IDH-1(7). IDH mutations were found in only 7% of patients with "de novo" primary GBM(7). Of interest for the imaging community, IDH mutations are associated with accumulation of 2-hydroxyglutarate (2HG) that can be detected as a small peak (multiplet) resonating at 2.25 ppm by H-MR spectroscopy(8).

Glioblastomas WHO-IV are driven by complex signaling pathways and are among the most aggressive and challenging neoplasms to treat. GBM grow fast by compressing adjacent functional brain tissue and dislocating white matter fascicules. Breakthrough in understanding of their molecular pathogenesis has stimulated the development of novel therapies, it has led to advancement of clinical trial design and identification of GBM subgroups with a more-favorable prognosis and response to therapy(9). Standard therapy for GBM involves maximal safe surgical resection followed by radiotherapy with concurrent TMZ (10).

MR is the standard tool to evaluate disease status in patients with glioma. With the introduction of new response criteria, both the enhancing component on post-contrast T1-weighted images and the T2-signal hyperintensity on FLAIR images must be considered when evaluating response to treatment. The new "Response Assessment in Neuro Oncology" (**RANO**) **criteria** were introduced only in 2010 and they are now the standard of care in clinical practice and they are used regularly in multicenter drug trials(2). Notwithstanding, identification of solid non-enhancing growing components of a tumor from other causes of FLAIR abnormality remains a challenge, especially in patients treated with radio and/or chemotherapy. Aspecific tissue alterations on FLAIR and post-contrast T1-weighted images may mimic tumor progression in the early post-treatment period 2-6 months after radiotherapy.

Twenty to 30% of GBM patients show transient increased contrast enhancement. **Pseudoprogression** is called this treatment-related reaction of the cancer leading to an increase in enhancement (*flare phenomenon*) and/or edema on MR imaging without increased tumor activity. Pseudoprogression

may occur within the first 12 weeks after radiotherapy and/or chemotherapy with TMZ, gene therapy, or intracavitary chemotherapy. Typically, the absence of true cancer progression is shown by stabilization or decrease in size of the lesion during follow-up between 3 and 6 months and without additional therapies. Pseudoprogression is associated with local tissue reaction: inflammation, edema and increased abnormal vessel permeability. It usually subsides without further treatment, but in some unfortunate cases it may progress over time into the more severe local tissue reaction with signs of mass effect in addition to disrupted BBB and edema. Delayed radiation necrosis usually occurs 3-12 months after radiotherapy.

Pseudoresponse is a marked decrease in contrast enhancement as early as 1 to 2 days after initiation of therapy. It commonly results in high radiological response rate of 25% to 60% (11) and 6 months progression-free survival (PFS-6), but with rather modest effects on overall survival (OS). Pseudoresponse is induced by new antiangiogenic drugs (bevacizumab, cediranib, irinotecan) that modify signal transduction through the VEGF signaling pathways. The first major trial of bevacizumab for GBM reported a 57% response rate and a PFS-6 of 46% (12). The rapid normalization of the BBB within 24 hours, rebound enhancement and edema on drug discontinuation with a rapid "re-response" after restart suggest that a pseudoresponse is responsible for the imaging and clinical response. These imaging changes are so rapid that are unlikely to depend on real tumor shrinkage. Macdonald criteria suggest that radiological responses should persist for at least 4 weeks before they are considered as true responses. Unfortunately, patients treated with anti-VEGF agents may develop progression of the nonenhancing tumor component as shown on FLAIR imaging (13). This unfavorable event may be the result of migration of glioma cells induced by antiangiogenic treatment.

MR spectroscopy, perfusion and diffusion tensor imaging, together with 11C-methionine Positron Emission Tomography (PET) have been proven useful in assessing response to therapy and in particular in differentiation of pseudoprogression from true tumor progression, and true tumor response from pseudoresponse.

References

1. Cha S. Update on brain tumor imaging: from anatomy to physiology. AJNR Am J Neuroradiol. 2006;27(3):475-87. Epub 2006/03/23.
2. Wen PY, Macdonald DR, Reardon DA, Cloughesy TF, Sorensen AG, Galanis E, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2010;28(11):1963-72. Epub 2010/03/17.
3. Pallud J, Taillandier L, Capelle L, Fontaine D, Peyre M, Ducray F, et al. Quantitative morphological magnetic resonance imaging follow-up of low-grade glioma: a plea for systematic measurement of growth rates. Neurosurgery. 2012;71(3):729-39; discussion 39-40. Epub 2012/06/07.
4. Pallud J, Mandonnet E, Duffau H, Kujas M, Guillevin R, Galanaud D, et al. Prognostic value of initial magnetic resonance imaging growth rates for World Health Organization grade II gliomas. Ann Neurol. 2006;60(3):380-3. Epub 2006/09/20.
5. Law M, Oh S, Babb JS, Wang E, Inglese M, Zagzag D, et al. Low-grade gliomas: dynamic susceptibility-weighted contrast-enhanced perfusion MR imaging--prediction of patient clinical response. Radiology. 2006;238(2):658-67. Epub 2006/01/07.
6. Marko NF, Weil RJ. A case for reclassifying infiltrating gliomas in adults. Journal of neuro-oncology. 2012;109(3):587-91. Epub 2012/07/21.
7. Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, et al. An integrated genomic analysis of human glioblastoma multiforme. Science. 2008;321(5897):1807-12. Epub 2008/09/06.
8. Choi C, Ganji SK, DeBerardinis RJ, Hatanpaa KJ, Rakheja D, Kovacs Z, et al. 2-hydroxyglutarate detection by magnetic resonance spectroscopy in IDH-mutated patients with gliomas. Nature medicine. 2012;18(4):624-9. Epub 2012/01/28.
9. Tanaka S, Louis DN, Curry WT, Batchelor TT, Dietrich J. Diagnostic and therapeutic avenues for glioblastoma: no longer a dead end? Nature reviews Clinical oncology. 2013;10(1):14-26. Epub 2012/11/28.
10. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. The New England journal of medicine. 2005;352(10):987-96. Epub 2005/03/11.
11. Batchelor TT, Sorensen AG, di Tomaso E, Zhang WT, Duda DG, Cohen KS, et al. AZD2171, a pan-VEGF receptor tyrosine kinase inhibitor, normalizes tumor vasculature and alleviates edema in glioblastoma patients. Cancer cell. 2007;11(1):83-95. Epub 2007/01/16.
12. Vredenburgh JJ, Desjardins A, Herndon JE, 2nd, Marcello J, Reardon DA, Quinn JA, et al. Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2007;25(30):4722-9. Epub 2007/10/20.
13. Norden AD, Young GS, Setayesh K, Muzikansky A, Klufas R, Ross GL, et al. Bevacizumab for recurrent malignant gliomas: efficacy, toxicity, and patterns of recurrence. Neurology. 2008;70(10):779-87. Epub 2008/03/05.