Syllabus Outline

SPECIALTY AREA – *Post-Treatment Brain Evaluation: Diffusion Techniques*

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HIGHLIGHTS –

1. Standard Diffusion techniques have been well studied and can provide insight into the microvasculature and microstructure of tumors and disease processes.
2. Less commonly investigated diffusion techniques (diffusion tensor imaging and intravoxel incoherent motion) and arterial spin labeling (ASL) may play a role in evaluating tumor physiology and vascularity without the need for an exogenous contrast agent.
3. Treated tumors may undergo vessel co-option and shift to a more infiltrative (and less angiogenic) pathophysiology, such that new infiltrating tumor components may manifest as, and correlate with areas of ADC map signal alteration.

TALK TITLE – The Post-Treatment Brain: Diffusion and Arterial Spin Labeling Techniques.

TARGET AUDIENCE – Radiologists, technologists, neuro-oncologists, translational researchers, and interested members of the healthcare team caring for neuro-oncologic patients.

OBJECTIVES – Attendees of this session will gain insight into the post-treatment behavior of common adult primary brain tumors with respect to tissue infiltration and tumor vascularity, and better appreciate how the interplay of these factors can affect subsequent image interpretation and clinical decision-making. The angiogenic and infiltrative pathophysiology evidenced by glioblastoma multiforme (GBM) will be presented, along with challenges in imaging these seemingly disparate tumor components, which are generally better characterized by advanced MR techniques. In this context, attendees will better appreciate how diffusion and perfusion techniques can provide complementary information in the context of competing pathophysiological tumor mechanisms.

PURPOSE – 17,000 newly diagnosed cases of Glioblastoma Multiforme (GBM) are identified per year, each with a poor prognosis and typically initially treated with surgery and chemoradiation. The post-treatment brain becomes a challenging radiological diagnostic dilemma for the medical community, as these employed therapies (surgery, chemo- and radiation therapy) may significantly change the landscape of any residual tumor and the otherwise presumably “normal” surrounding brain tissue, complicating interpretation by conventional radiographic studies. In addition, correct interpretation of GBM MR imaging studies are compromised by multimodality treatment effects rendering difficult differentiation of tumor growth/recurrence from pseudoprogression, pseudoresponse and radiation necrosis, which may in part be related to alteration in tumor vascularity and pathophysiology, surrounding edema, and treatment effects.

Advanced MR techniques can better evaluate the physiological parameters of the tissue of interest and can provide additional diagnostic information, not otherwise available via conventional, morphological imaging alone. In this context, we examine the role that various diffusion techniques and ASL might play in the evaluation of the post-treatment brain.

METHODS – An overview of the pertinent literature describing various diffusion techniques, as applied to intracranial tumor imaging, will be performed with a primary focus on standard single-shot echo planar imaging (ssEPI) diffusion weighted imaging (DWI) techniques, the derived apparent diffusion coefficient (ADC) map, and associated post-processing methods. Additionally, alternate diffusion techniques including diffusion tensor imaging (DTI) and intravoxel incoherent motion (IVIM) will be presented, followed by a discussion of arterial spin labeling methodology, acquisition techniques, and the applicability of these techniques in evaluating the post-treatment brain.

RESULTS – Several studies have been performed to assess the utility of DWI, and more recently DTI in evaluating and monitoring cancer therapy. Diffusely infiltrative malignant gliomas typically invade adjacent tissue and extend beyond the abnormalities identified on conventional MRI, in contrast to intracranial metastatic tumors[1-4]. Evaluation of ADC values in the nonenhancing peritumoral regions of T2-hyperintensity can help distinguish high-grade gliomas from metastases, with generally lower values in infiltrated peritumoral areas of primary neoplasms compared with metastases[5]. While derived ADC values may have a limited role in differentiating high-grade astrocytomas from surrounding peritumoral edema[6], studies have suggested that interrogation of the peritumoral region can aid in monitoring treatment[7, 8, 9].

DTI-derived parameters (mean diffusivity and fractional anisotropy) of the enhancing and peritumoral regions of GBM and metastatic tumors can act to aid in differentiating these entities, in monitoring therapy[10], and in differentiating residual/recurrent tumor from pseudoprogression, pseudoresponse, and radiation injury[11], although mixed results have been reported[12]. Physiologically, increase in DTI-derived mean diffusivity is similar to the finding of increased DWI-derived ADC values in peritumoral region of metastases compared with high-grade gliomas.

ASL, an emerging MR perfusion technique that requires no exogenous contrast agent or radiation exposure[13], possesses some advantages over DSC/DCE MRI and FDG PET in the evaluation of brain tumor perfusion[14, 15], and is a valid method of assessing microvascular perfusion that can distinguish *de novo* high-grade from low-grade gliomas[16, 17-19, 20], with nice agreement between intratumoral CBF between the DSC and ASL perfusion methods[21]. ASL is minimally influenced by disruption of the blood brain barrier, making it an attractive option when compared with DSC-derived CBF maps, and provides absolute quantification of *cerebral blood flow* (CBF), allowing comparison of values in a given individual patient over time.

There are many clinical iterations of ASL, and some demonstrate relative insensitivity to microvascular permeability effects, which may be helpful to evaluate enhancing lesions following surgical resection, and can confound DSC MRI analysis of enhancing tumors[17, 22]. ASL, like DSC, may be a sensitive biomarker of tumor behavior in patients on angiogenic therapy in the setting of both non-enhancing infiltrative tumor progression as well as new enhancing glioma[23]. ASL can be helpful in predicting treatment outcome in brain metastases[24], differentiating GBM from radiation necrosis[25], and in predicting progression-free and overall survival[26].

DISCUSSION – Understanding the components that contribute to the observed increase in peritumoral FLAIR signal volume (potentially representing a combination of tumor recurrence/progression, edema and gliosis) at the resection and original tumor site is of utmost importance. A shift in tumoral pathophysiology occurs such that tumors initially reliant on angiogenesis may shift to a more diffusely infiltrative nature harnessing their blood supply by growing along normal perivascular spaces[27] in a

process termed "vessel co-option". As the tumor continues to grow using vessels with an intact blood brain barrier, it will not be detected by conventional gadolinium contrast-enhanced T_1-weighted imaging[9, 28]. In recognition of this, the recently proposed RANO and Levin criteria have incorporated the volumetric measure of peritumoral T2/FLAIR signal abnormality when assessing disease progression[29].

Diffusion signal alteration, evidenced by changes in ADC, represents one metric that may reflect infiltrative tumor progression in regions of increasing FLAIR abnormality and may correlate with recurrent tumor, based on the observation that significantly lower ADC represents increased tumor cellularity. In tumors undergoing vessel co-option and a more infiltrative pathophysiology, the new infiltrating tumor components manifest as FLAIR signal abnormality extending from the site of the original enhancing tumor mass, and correlate well with areas of ADC map signal alteration.

At least two distinct subtypes of glioma tumor recurrence exist. In one subset of patients, neo-angiogenic tumor reemerges as evidenced by recurrent contrast enhancing tumor. In the second subset, recurrent tumors appear to undergo differentiation into a more infiltrative, non-angiogenic tumor subtype. The role of perfusion imaging in evaluating underlying tumor vasculature in patients undergoing anti-angiogenic therapy (such as bevacizumab and cediranib) has been described in the context of vascular normalization, including pre-existing vessel pruning, resulting in the recession of endothelial fenestra, suppression of vascular sprouting, and reduction in blood flow and vessel patency. Thus, tumor enhancement, by itself, is a relatively insensitive biomarker for assessing intracranial lesion burden, especially in the setting of anti-angiogenic therapies, and may lead to a false negative assessment of the true presence of residual/recurrent tumor (pseudo-response). Viable tumor can still be present and progressing in spite of the absence or regression of enhancement.

Perfusion imaging has historically played a pivotal role in assessing how a given patient will respond to angiogenic therapy. ASL is a promising MRI perfusion technique that has some comparative advantages over DSC/DCE MRI and FDG PET. However, like with DSC PWI, not all ASL techniques are comparable, and a healthy degree of skepticism is suggested regarding the any conclusions that might be drawn at this time, since technique standardization is needed.

CONCLUSION – The post-treatment brain presents a challenge to MR imaging, especially in patients treated with anti-angiogenic therapy. An understanding of the therapeutic effects on *vascular metamorphosis*, and how *anti-angiogenic therapies* might alter both the imaging characteristics and the underlying tumor behavior, as well as potential mechanisms of tumor escape is important to correctly interpret imaging findings. Gliomas appear to progress by harnessing non-VEGF driven angiogenic pathways for growth, or switch to a non-angiogenic infiltrative tumor subtype.

Perfusion imaging may prove useful in defining increased perfusion associated with angiogenic tumor recurrence, and ASL offers a compelling adjunct in evaluating vascular changes in the post-treatment brain. More infiltrative recurrent disease has the potential to remain occult to detection by perfusion metrics alone and ADC may play a more significant role in evaluating the post-treatment brain.

KEY DEFINITIONS –

- **Pseudoprogression:** The appearance of a new or enlarging contrast-enhancing lesion within the radiation field, at the primary tumor surgical site, typically within the first six months following completion of radiotherapy, that spontaneously subsides over serial MRI scans without change in chemotherapy or initiation of new therapy.
- **Radiation Necrosis:** The presence of gadolinium-enhancement mimicking tumor recurrence or

progression within the post-radiation field typically occurring nine-to-twelve months and thereafter[30].

- **Pseudoresponse:** The continued presence of residual or recurrent tumor that otherwise demonstrates interval decrease or disappearance of tumor enhancement on conventional anatomic gadolinium-enhanced MR images as early as 12-24 hours following the administration of anti-angiogenic treatment[29].
- **Vessel co-option:** The shift in tumor physiology such that tumors initially reliant on neo-angiogenesis may shift to a more infiltrative nature, harnessing their blood supply by growing along perivascular spaces.

References

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