Beyond Enhancement and Histology: Molecular Markers for Diagnosis

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Purpose
Clinical care and outcome in Glioblastoma (GBM) remains challenging due to the tumor's invasive growth. To establish personalized treatment options in GBM, discovery of genetic mechanisms essential for the tumor's invasion is needed. We have previously described radiogenomic approaches to diagnose gene networks non invasively by analyzing genomic data from TCGA. The purpose of the current research is to identify a genetic network that drives GBM invasion and can be targeted specifically.

Method and Materials
Using Kaplan-Meier statistics, the data of the two independent databases TCGA and REMBRANDT were used to validate the genetic network's impact on clinical outcome. The genes' status was assessed in a panel of human glioma stem cells (GSCs) and conventional proneural, classical and mesenchymal GBM cell lines using RT-PCR. Differentiation potential (Tuj1+ve, S100A+ve, and GFAP+ve), self-renewal (limiting dilution assays), invasion (Boyden chamber) and proliferation (BrdU) were assessed. Gain (lentiviral vectors) and loss (SMARTchoice Inducible shRNA) of function experiments were performed. Orthotopic xenograft models (nude mice) were used to characterize the genes impact in vivo. Potential FDA approved therapeutics were identified using connectivity map.

Results
Texture analysis based on radiogenomics significantly predicted the genes responsible for invasion of GBM in a non-invasive manner. Invasion in both, in vitro and in vivo was significantly decreased upon downregulation of this gene network. Transcriptome microarray analysis showed that an upregulation of the described genes results in class switching from proneural to mesenchymal subtypes. Cmap derived therapeutics could significantly inhibit the gene network's activity and hence invasion.

Conclusion
The described genes could be essential drivers of molecular subtypes and invasion in GBM. The therapeutics defined with cmap offer a targeted therapy to address these key features of GBM pathogenesis. Noninvasive radiogenomics-based identification of tumor subgroups and potential treatment approaches can significantly contribute to personalized therapy.

Clinical Relevance/Application
The described gene network seems to be key for GBM pathogenesis. Noninvasive, radiogenomics-based subgroup identification and specific novel treatment approaches can significantly contribute to personalized GBM therapy.

Radiogenomic Analysis of TCGA/TCIA Diffuse Lower Grade Gliomas by Molecular Subtype

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To investigate relationships between imaging phenotype and genetic classification of LGGs in the TCGA/TCIA database, we analyzed semi-quantitative MR features and IDH1/1p19q classifications.

METHOD AND MATERIALS
Pre-operative MRIs of 72 TCGA/TCIA LGGs were reviewed by 3 neuroradiologists blinded to molecular status, using the VASARI LGG feature-set (standardized set of 26 MRI features). Data were compiled across 3 readers to define a single measure per sample. Clinical and molecular classifications were obtained from the LGG-AWG marker paper (TCGA Research Network.NEJM;2015, in press). Associations with histology, WHO grade and molecular type were assessed by Fisher's exact test (categorical features) and ANOVA/t-test (continuous features).

RESULTS
Of 70 tumors with IDH1/1p19q classification, 16 were IDHmut-codel, 34 were IDHmut-non-codel, and 19 were IDHwt. IDHmut-codel tumors were preferentially centered in the frontal lobes (75%, FET p=0.026). IDHmut-non-codel tumors tended to arise in frontal (41%) and temporal lobes (41%), while IDHwt tumors did not show preference. Nonenhancing tumor margins were more well-defined for IDHmut LGGs (56% and 76% were well-defined) than for IDHwt tumors (32%, FET p=0.027). 66% of LGGs had an enhancing region, but this was not associated with molecular class (FET p=0.286), although enhancement was more likely in grade III than grade II (FET, p=0.043). 23% of these grade II/III tumors had MRI evidence of necrosis, with presence equally likely in any of the 3 molecular classes (FET p=0.931); however, 5/16 (31%) of LGGs with necrosis on MRI were grade II. IDHwt tumors tended to be smaller than IDHmut tumors (23.0 cm² vs 39.7cm², respectively, for maximal area, t-test p=0.001). Further differences were found in T1/FLAIR ratio (FET p=0.030), T2/FLAIR signal crossing the midline (FET p=0.007), and presence of hemorrhage (FET p=0.009), cysts (FET p=0.006), or satellites (FET p=0.030).

CONCLUSION
Review showed differential MR features between LGG molecular classes. IDHwt LGGs had association with aggressive features (e.g., small dimension with poorly-defined non-contrast-enhanced borders). Lack of association with necrosis or presence of an enhancing region suggests that the IDHwt class is not simply underdiagnosed GMB. An investigation of imaging profiles that align with molecular type or define further subclasses is underway.

CLINICAL RELEVANCE/APPLICATION
Differential MR features exist between LGG molecular classes.

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Daniel L. Rubin, MD, MS - 2012 Honored Educator
Daniel L. Rubin, MD, MS - 2013 Honored Educator

The Triple-Negative Low-Grade Glioma: MR Imaging Correlates of Aggressive Molecular Phenotype

Wednesday, Dec. 2 9:25AM - 9:35AM Location: E451A

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PURPOSE
Low-grade gliomas (LGGs) are a heterogeneous group of tumors with distinct clinical behavior and prognosis. One strategy to improve their characterization is with molecular biomarkers: P53, IDH 1/2, and 1p19q. These objective markers correlate with histologic classification and clinical outcomes. Specifically, the absence of IDH1/2 mutation or 1p19q deletion have been identified as indicative of a poor prognosis. The purpose of our study was to determine MR imaging parameters that can discriminate a, recently-described, aggressive subtype of LGG that is characterized by an absence of all three of these genetic alterations.

METHOD AND MATERIALS
A retrospective review of our medical records from 2010 to 2014 yielded 105 cases of pathologically-confirmed LGG that had molecular testing for P53 mutation, IDH1/2 mutation, and 1p/19q deletion. The MR imaging characteristics including tumor location, volume, infiltration pattern, cortical involvement, hemorrhage, contrast-enhancement, and quantitative diffusion and perfusion were
assessed. Additionally, clinical data of patient treatment, disease course, and survival was collected.

RESULTS
There were 24 diffuse astrocytomas (23%), 36 oligoastrocytomas (34%) and 45 oligodendrogliomas (43%). PS5 mutation was found in 21 (20%), IDH1/2 mutation was found in 70 (67%), and 1p19q deletion was found in 45 (43%). Thirteen cases (12%) did not have any of these genetic alterations. Triple-negative tumors showed a lower incidence of cortical involvement (p<0.05) and lower mean and minimum apparent diffusion coefficient (ADC) values (1.25 vs 1.45x10^-3 mm^2/s; 0.89 vs 1.09x10^-3 mm^2/s, p<0.01). Multiple logistic regression analysis showed low ADC value as an independent predictor of triple-negative LGG. With a cutoff of 1.0x10^-3 mm^2/s, ADC value provides a 73% sensitivity and a 72% specificity with an odds ratio of 7.0 (p<0.01). In cases with available clinical follow-up, triple-negative LGGs were found to have disease progression within 2 years in 50% compared to 16% in the non-triple-negative cohort.

CONCLUSION
Triple-negative LGGs are a clinically and biologically aggressive phenotype that exhibit lower mean ADC values and lack of cortical involvement on MR imaging.

CLINICAL RELEVANCE/APPLICATION
MR imaging features can be used alongside molecular biomarkers to assess the aggressiveness and prognosis of LGGs and subsequently may provide a means of guiding management as patient-tailored therapy.

RC505-06 Do Macrocyclic Gadolinium Based Contrast Agents(GBCA) Deposit Gd in Normal Brain Tissue in Patients Receiving Contrast Enhanced MRI?

Wednesday, Dec. 2 9:35AM - 9:45AM Location: E451A

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PURPOSE
Based on T1 shortening on noncontrast MR, recent studies have suggested that small amounts of gadolinium(Gd) may accumulate in brain even in patients with normal renal function. Recently McDonald confirmed Gd deposition in postmortem human brain tissue. To date, studies have shown Gd brain deposition only with Group 1 linear agents. The purpose of this study was to determine whether Gd is deposited in brain among patients receiving more stable macrocyclic agents using postmortem tissue analysis with inductively coupled plasma mass spectrometry (ICP-MS).

METHOD AND MATERIALS
This study was approved by the IRB. Brain tissue was collected at autopsy from decedents with available medical records that document past history of MRIs with or without GBCA exposure. Decedents with no prior MRI or only nonGd MRI served as controls. Tissue samples were collected from white matter, putamen, globus pallidus, caudate nucleus, pons and dentate nucleus and analyzed for Gd using ICP-MS. Bone tissue from rib was also analyzed as a reference tissue in each case. Results were correlated with types of agent received, cumulative dose, time since dosing and clinical and laboratory data.

RESULTS
Among 21 cases obtained to date, 15 cases with normal renal function received 1 or more GBCA exposures and 6 cases had no exposure. ICP-MS showed measurable amounts of Gd deposition (range 0.003-3.54ng/mg) in all 15 cases receiving GBCA. A subset of these, 4 cases received only a macrocyclic GBCA(1 Gadavist ; 3 ProHance) with doses ranging from 10 to 126 ml and Gd was also detected in all macrocyclic cases (0.006-0.188 ng/mg). Gd in brain was detected after only a single dose and deposition was present among all brain regions sampled. Gd deposition in rib was also positive in all 15 cases and showed significantly higher levels than brain in each case. By comparison there was no detectable Gd in any control cases.

CONCLUSION
Gd deposition occurs in normal brain tissue in patients with normal renal function with a past history of GBCA exposure even in those receiving only macrocyclic agents. The clinical significance remains undetermined and we are pursuing further investigation.

CLINICAL RELEVANCE/APPLICATION
Gd deposition is present in normal brain tissue after only one dose even with macrocyclic agents. This important observation needs further investigation to determine potential toxic effects.

Handout:Nozomu Murata


RC505-07 Post-therapy Brain Tumors: Imaging Pitfalls and Strategy

Wednesday, Dec. 2 9:45AM - 10:10AM Location: E451A

Soonmee Cha, MD, San Francisco, CA (Presenter) Nothing to Disclose

LEARNING OBJECTIVES
1) Discuss biologic and pathologic complexity of post-therapy brain tumors. 2) Present latest advances in imaging methods to differentiate recurrent tumor and treatment effect. 3) Review strengths and pitfalls of imaging post-therapy brain tumors. 4) Describe imaging strategy to improve diagnosis and management of patients with treated brain tumor.

RC505-08 Directions, Protons and Flows - Practical Advanced Brain Tumor Imaging
RESULTS
A total of 58 biopsy sites were obtained. Overall, cellularity demonstrated moderate linear correlation with T1W-postcontrast (r = 0.76), FLAIR (r = 0.62) and ADC (r = 0.64, within nCE region only). Multiple linear regression combining all three variables yielded a model highly predictive of cellularity, both within the nCE (r = 0.93) and CE (r = 0.76) region. Within the nCE region, the model weighted ADC (p = 0.0072) and FLAIR (p = 0.058) more significantly than T1W (p = 0.83), as determined by analysis of variance (ANOVA). Within the CE region, T1W (p < 0.001) and FLAIR (p = 0.12) were weighted more significantly than ADC (p = 0.21).

CONCLUSION
A multiparametric model combining T1W-postcontrast, FLAIR and ADC values strongly predicts cell counts in GBM, notably with correlation >90% in the nCE region. By applying this model at each voxel within the tumor volume, a noninvasive map of cellular density can be generated.

CLINICAL RELEVANCE/APPLICATION
Cellularity maps of the peritumoral region in GBM localize tumor microinvasion and may be used as a tool to guide extended surgical resection or biopsy and to assess infiltrative tumor burden.

RC505-11 Receiver Operating Characteristic (ROC) and Logistic Fit Analysis for Detecting Brain Tumor Based on OEF Measurements Obtain by PET and MR

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PURPOSE
Receiver operating characteristic (ROC) curve and logistic fit analysis for detecting brain tumors using cerebral oxygen extraction fraction (OEF) measurement obtained by [15]O positron emission tomography (PET) and oxygen sensitive magnetic resonance (MR) imaging.

METHOD AND MATERIALS
30 participants (20 with brain tumors) were recruited. MRI included standard clinical sequences plus OEF-MRI; a two-dimensional multi-echo gradient spin echo sequence. Concurrent with the MR acquisition, subjects with brain tumors underwent PET scanning, which included 2 sets of 3 scans with serial inhalation of air with 40-75 mCi [15]O labeled carbon monoxide , 40-75 mCi [15]O labeled oxygen , and injection of 25-50 mCi [15]O labeled water. MR and PET data were post-processed off line and registered to the anatomic T1 pre- and post-contrast images. Regions of interest were drawn based upon contrast-enhancing tumor areas, contra-lateral normal white matter (NWM), and normal gray matter (NGM) Ratios of OEF (rOEF) were obtained for lesions compared to normal tissue. Statistical analyses, including Bland-Altman plot, ROC, and logistic fit, were performed.
RESULTS

Bivariate analyses results are: between two rOEF-PET measurements of all selected regions R=0.92 and P <0.0001, and tumor type R=0.68 and p<0.0001; and similarly between rOEF-MR and rOEF-PET all selected regions R=0.3 and P <0.0413, and tumor type R=0.39 and p<0.173. Based on Bland-Altman analysis both MR and PET methods of obtaining OEF are in agreement (the measurements lie within range ±1.96xSD). However, the coefficient obtain for rOEF-MR covers much larger range which may not be clinically acceptable. Area under ROC curve (AUC) has much higher value for PET (0.95) than MR (0.58).

CONCLUSION

Both MR and [15]O PET can measure OEF in brain tumors and in peritumoral edema. Variable OEF measurements for tumor and edema may be implication for tumor grade and prognosis. BOLD MR fails in regions with signal loss on SWI or T2*. Area under ROC Curve (AUC) has much higher value for PET (0.95) than MR (0.58). Based on logistic fit probability of distinguishing tumor with PET is much higher than MR.

CLINICAL RELEVANCE/APPLICATION

Both MR and PET techniques have tremendous potential and may offer new insight into the underlying physiology of brain tumors and their response to therapy without requiring radiation or injected contrast. BOLD MR fails in regions with signal loss on SWI or T2*.

PURPOSE

Ferumoxytol, an ultrasmall iron oxide nanoparticle (USPIO) has been marketed as Feraheme® for iron replacement therapy in patients with chronic kidney disease. Due to its magnetic properties, and long plasma half-life, ferumoxytol uniquely allows MR imaging of the intravascular space early after injection, which is beneficial for high-resolution blood volume mapping of brain lesions. Delayed (24h) ferumoxytol enhancement may help in differential diagnosis. As of March 30, 2015, the FDA added a boxed warning to Feraheme® package insert, which strengthens existing warnings regarding potential fatal and serious hypersensitivity reactions including anaphylaxis, even in patients who received Feraheme® previously. It emphasizes the importance of trained personnel, monitoring at least 30 min post injection to properly treat hypersensitivity reactions.

METHOD AND MATERIALS

Our institution has been actively doing imaging research with ferumoxytol for over 10 years. In this study we evaluated early adverse events (occurring within 1 day), potentially related to ferumoxytol administration hypersensitivity, and qualitatively compared it with published data.

RESULTS

At the time writing this abstract we have analyzed a total of 553 ferumoxytol infusions in 298 patients and have not recorded any severe (grade 3, 4 or 5) hypersensitivity reactions occurring within 1 day. Early grade 1 and 2 reactions, were present, such as nausea/vomiting (5.1%), hypertension (3.3%), pruritus (1.3%). In published data, the frequency of severe hypersensitivity of Feraheme® was equivalent to ionic iodinated contrast media, and about 10x higher than gadolinium MR contrast agents and nonionic iodinated contrast agents.

CONCLUSION

Our results suggest less frequent severe hypersensitivity reactions compared to published data, and it may be due to the difference in patient population. A detailed toxicity evaluation of our data is in progress. The intended purpose of change in labeling by the addition of the boxed warning is to strengthen the warnings in the label and to mitigate the risk of serious hypersensitivity reactions including anaphylaxis in order to enhance patient safety.

CLINICAL RELEVANCE/APPLICATION

Ferumoxytol remains safe for MRI in the vast majority of patients, with a very small risk of serious adverse event, and personnel should be prepared to treat such reactions if they were to occur.