Key words: Global health, health disparities, disruptive innovation

References:

56 Comparison of Arterial Input Functions by Magnitude and Phase Signal Measurement in DCE MRI of brain cancer patients
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Purpose: The aim of this work is to (1) investigate the accuracy and robustness of magnitude and phase-derived arterial input functions (AIF) as compared to “gold standard” volumetric DCE-CT; and (2) evaluate the impact of individualized magnitude and phase signal AIF measurements on resulting perfusion parameter maps using a common 4D temporal dynamic analysis (TDA) method in metastatic brain cancer patients treated with stereotactic radiosurgery.

Methods: We evaluated 14 brain metastases imaged with volumetric DCE-CT (Toshiba, Aquilion ONE) and DCE-MRI (MRIS 3T Verio) at baseline then 7 and 21 days post-radiosurgery. Both variable-flip-angle (VFA) T1 measurements and dynamic imaging used 3D-FLASH with matched TE/TR of 1.8/4.8ms, with 1x1x5 mm voxels. Voxel-based whole brain TDA was performed on all data using in-house software to: (1) compare the AIF curve from DCE-CT using the internal carotid artery (AIF) and sagittal sinus (VIF) curve from the DCE-CT against DCE-MRI [magnitude (VIFmag) and phase-based (VIFph)] and (2) compare kinetic parameters area under the curve (AUC) and Ke,ass, assuming the Modified Tofts model when using individual CT AIF, MRI Magnitude and Phase-based VIF (Sagittal Sinus) and population-based AIF as well as individual voxel-based T10 maps versus assumed T10 = 2400 msec.

Results: The AUC of individual AIF and VIF on DCE-CT were similar and resulting median Ke,ass (0.048 +/- 0.03 s^-1) was also similar. For DCE-MRI, using measured voxel-based T10 maps, the resulting Ke,ass was higher than for CT using individual VIFmag (0.181 +/- 0.11 s^-1) or VIFph (0.121 +/- 0.099 s^-1). This is likely resulting from the smaller AIF peak since the population AIF (which more closely resembles CT) correlates better to DCE-CT metrics. The measured median T10 value was 1572 +/- 594 (n=41) and using the assuming T10=2400 ms resulted in significantly higher Ke,ass (0.3 +/- 0.14 s^-1) and AUC (p=0.0006). Voxel-wise correlation between Ke,ass values than from CT and MRImag,T10 resulted in high R^2 values (~0.5, p<0.05) for all imaging days and showed good interchangeability (see Bland-Altman plot in Figure 1).

Conclusion: This preliminary data highlights the stability of DCE-CT calculations as well as susceptibility of DCE-MRI Ke,ass measurements to various imaging factors, including AIF selection and T10 values used in the model. Using the same voxel-based analysis platform for both DCE-CT and MR significantly improved correlation values confirming the need to take into account tumor heterogeneity when assessing functional data.

Keywords: Brain metastases, biomarker, perfusion imaging
Focal adhesion signaling and therapy resistance in cancer
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Purpose: Intrinsic and acquired resistance of tumor cells to therapy originates from multiple avenues. One avenue includes extracellular matrix (ECM) and proteins that facilitate cell interaction with ECM. These focal adhesion (FA) proteins coalesce at specific membrane sites as large multiprotein complexes functioning as signaling hubs and structural nexus. Molecular targeting of various FA proteins has shown promising preclinical data. Even more interesting are rather recent findings about activation of prosurvival bypass signaling under specific inhibition of integrins and their dependence on ECM stiffness.

Materials/methods: Different tumor models were investigated such as head and neck, pancreatic ductal carcinoma, glioblastoma. We performed a systematic targeting of FA proteins using siRNA or antibodies where applicable. In-vitro and in-vivo survival assays and a variety of mechanistic studies were conducted.

Results: To date, integrins turned out as most promising druggable candidates. Most interesting, molecular targeting generally showed to prominently induce unfavorable prosurvival signaling. Multitargeting strategies were successful to abrogate this bypass signaling and optimize radiochemosensitization.

Conclusions: Integrins and other FA proteins are promising cancer targets. Understanding of underlying mechanisms is still the needle eye. From our data, multitargeting approaches on top of conventional radiochemotherapy look beneficial as specific tumor cell functions can be inhibited.

Keywords: Focal adhesions, resistance, bypass signaling

References: