Translational MRI/MRS of Cancer

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Highlights:

- Translational MR in cancer involves studies from the bench-to-bedside.
- MR studies of cancer cells aid in understanding the metabolism and energetics of cancer.
- Ex vivo studies on extracted tissue samples play a pivotal role in metabolomics.
- In vivo MRI/MRS studies on animal tumor models have helped in the development of new contrast mechanisms as well as understanding of tumor physiology and metabolism.
- Development of high field clinical magnets and faster image acquisition methods have led to translation of methods developed in animal models into the clinic.
- Re-designing MRI/MRS methods in animal and model systems to better understand the mechanism of the observations made in the clinic completes the circle of translational MR methods in cancer.

This introductory lecture is geared towards “beginner” level scientists, who are interested in translational MR studies in cancer either going from bench-to-bedside (pre-clinical to clinical) or back. The presentation will provide an overview of the advantages and challenges associated with translational MRI/MRS studies in cancer cells, ex vivo studies of tumor tissue samples, in vivo pre-clinical models as well as human studies in vivo.

Most MR studies on cancer cells have focused on understanding the metabolism of cancer cells during cell differentiation and proliferation or changes therein in response to cytotoxic and cytostatic agents. MRS studies of cancer cells typically involve experiments on cell extracts and cell pellets or more realistic studies on cells grown on agarose beads, hollow fibers and bio-reactors. While these studies provide an in-depth knowledge of the tumor cell metabolism, they do not mimic the “real” tumor as host-environmental factors cannot be studied with these models.

Metabolic phenotyping of tumor tissues is typically performed on biopsy samples or extracted tumor specimens. Earlier studies on tissue samples involved tissue characterization via high resolution MRS of aqueous and lipid soluble extracts. More recent studies involve magic angle spinning MRS studies of intact tissue samples. Phenotyping of the tumor tissue involves metabolomics as well as correlative studies with genomic and proteomic analysis. While these studies provide a wealth of information at extremely high spectral resolution and aid in the characterization of a tumor, they suffer from limitations similar to that of cell studies. In addition, the information is static in nature and dynamic studies of tumor metabolism and physiology cannot be performed. Since the extracted tissue represents only a small fraction of the tumor, these methods also suffer from sampling errors and cannot assess tumor heterogeneity.

Animal models play an essential role in translational MRI/MRS research and are the most realistic models of human tumors. These tumor models are used in developing bio-markers for cancer diagnosis and have also played a pivotal role in the development of MRI and MRS

methods for monitoring treatment response. Most commonly used animal models are tumor xenografts implanted subcutaneously; however, orthotopic tumor xenografts as well as models of spontaneous tumor growth are also being studied. Due to differences in tumor-to-body burden and associated differences in tumor perfusion in animal models versus human tumor, the challenge remains in the proper choice of tumor models so that the MRI/MRS techniques developed in animal models can be translated into the clinic. We will address some of these issues including quantitative DCE-MRI and diffusion imaging studies in cancer models as these methods necessitate high spatial and temporal resolution data and are highly sensitive to motion-induced artifacts. We will discuss applications of DCE-MRI as a surrogate marker of blood flow and hypoxia in tumor models and provide a historical perspective of how the ongoing studies on diffusion imaging of cancer models have translated into its use as an imaging biomarker of response assessment in the clinic. Newer contrast mechanisms including amide proton transfer (APT) or chemical exchange saturation transfer (CEST) are also being tested in animal models for cancer diagnosis, differentiation of tumor recurrence from radiation necrosis and to image protease activity in vivo. Since these techniques can be easily performed on clinical magnets, they hold a promising future in translational MRI studies of cancer.

Due to the non-invasive nature of MRI/MRS studies, a majority of the techniques developed in pre-clinical models of cancer have been seamlessly translated in the clinic and some of them including diffusion and perfusion imaging are routinely used for assessing human tumors. Although motion induced artifacts continue to pose a challenge for assessing tumors outside the brain, recent developments have led to widespread use of DCE-MRI and diffusion weighted MRI in assessing tumor hemodynamics as well as detection of tumor metastases using these methods. Clinical MRS methods suffer from relatively poor sensitivity compared to MRI as metabolites only in the mM range or above can be detected. However, MRS provides increased specificity to metabolic processes and both steady state as well as kinetic analysis of cancer metabolism can be studied in humans using ^{1}H, ^{31}P, ^{19}F or ^{13}C MRS. Major advances have been made in the recent years to make high spatial and temporal resolution MRS studies feasible and clinical trials involving hyper-polarized ^{13}C MRS of human cancers are currently being pursued at major academic centers.

Translational studies from humans to animal models or cell systems are necessary when a mechanistic understanding of observations made during clinical MRI/MRS is desirable. For example, development of choline kinase inhibitors as potential cancer therapeutics in animal models was largely due to the observation of elevated choline in most human cancers. Similarly the utility of the tau_i parameter, derived from the shutter-speed analysis of human DCE-MRI studies as a marker of cancer aggressiveness, led to mechanistic studies in cells and animal tumor models implicating the role of tau_i as a marker of energetics and hypoxia.

In summary, this is an exciting era for translational MRI and MRS studies in cancer and the studies on model systems truly complement the observations made in the clinic and help in better understanding of cancer biology. The recent advances in the development of targeted contrast mechanisms as well as metabolic phenotyping in vivo may aid in more sensitive MRI/MRS methods for detecting pre-malignant cancers or assist in adaptive therapy of cancer.