Predictive MRI Biomarkers to Assess Therapeutic Outcome in Cancer

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Target audience: Radiologists, MRI physicists and students interested in oncologic imaging.

Objectives
1. To understand the concept of "biomarker".
2. To review current trends in new anticancer biologic therapies.
3. To review current imaging algorithms used to define tumor response, and their limitations.
4. Review the scientific evidence of novel MRI-based algorithms used to assess tumor response.

Background: A biomarker is defined as *"a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention"* [1]. Imaging biomarkers are non invasive (for example when using MRI) compared to tissue sampling, and can interrogate the exact disease focus unlike blood measurement. Moreover, imaging biomarkers are easy to use for follow-up as opposed to repeat tissue sampling.

Current algorithms for assessing tumor response: Most current tumor response algorithms rely on changes in tumor size based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. guidelines. However, changes in size may be slow with the increased use of biologic therapies (antiangiogenic therapy, immunotherapy) and these guidelines do not take into account changes in tumor vascularity or necrosis. Therefore, response based on size changes may not be achieved by the new therapies, especially in the few weeks following therapy, as tumor shrinkage may be delayed. In fact, certain therapies may induce an increase in tumor size in patients responding, due to intratumoral edema, hemorrhage or necrosis. Therefore, better criteria adapted to these new therapies should be developed.

Role of advanced MRI methods:
Functional imaging, unlike anatomic imaging, provide information on tumor viability, cellularity, vascularity and metabolism [2]. These changes can be detected earlier than anatomic changes and are more applicable in assessing treatment response to new biologic therapies. Tumor angiogenesis, cell density/necrosis and changes in glucose metabolism can be imaged using DCE-MRI, DWI and FDG-PET, respectively. In this presentation, we will focus on DWI and DCE-MRI for assessing response to therapy. We will discuss in detail the data available for the use of DWI and DCE-MRI in different types of tumors, as well as their limitations.

DWI: DWI is increasingly applied to evaluate tumor response to chemotherapy, radiotherapy and locoregional therapy [3, 4]. Pre-clinical and clinical data have shown that effective tumor treatment results in an ADC increase, which can occur prior to any change in tumor size [5]. Transient reduction in ADC within 24-48 hours after initiation of treatment has been observed, possibly secondary to acute cell swelling or possibly reduction of interstitial volume [6]. Following the increase in ADC with treatment, the ADC will subsequently fall, related to tumor repopulation, fibrosis or tissue remodeling and decreased perfusion [3, 7, 8]. The rabbit VX-2 tumor model is one of the most widely studied. Tumor necrosis corresponded to higher ADC values compared with viable tumor [6, 9].

DCE-MRI [10]: DCE-MRI can provide information about tissue blood volume, perfusion and permeability. We will only discuss T1-weighted DCE-MRI in this presentation, as there is limited published data on the use of T2*-weighted dynamic susceptibility contrast-enhanced MRI (DSC-MRI) outside the brain. Perfusion parameters can be expressed as model free/semiquantitative (time to peak, AUC60 s, slope etc.) or can be expressed using a mathematical model, such as the Tofts or modified Tofts model.
There are multiple published studies showing a decrease in measured tumor Ktrans after antiangiogenic therapy. It has been suggested that pretreatment DCE-MRI parameters can predict radiation response in certain types of tumors, such as cervical cancer and renal cell carcinoma. In metastatic renal cell carcinoma treated with sorafenib, higher pre-treatment Ktrans was also a predictive marker of response to therapy.

Future directions:
PET-MRI: the combination of powerful techniques such as FDG-PET and functional MRI methods in a single acquisition will provide additional information on tumor response, which may be of great clinical benefit.

References

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